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REMARKS

Reconsideration and allowance are respectfully requested.

Claims 15-32 are pending and are at issue. Claim 15 has been amended to clarify further that the GLP-1 like peptide is insulinotropic. Newly added claim 21 finds support in previously pending claim 15. Newly added claims 22-32 find support in the originally filed claims, and the specification as filed. See e.g., page 3, lines 20-26 in the specification as filed. No new matter has been added.

OBJECTION TO THE SPECIFICATION

The Examiner objected to the specification as failing to provide antecedent basis for the word "infusion".

The objection is respectfully traversed, and reconsideration is requested.

Applicant directs the Examiner's attention to the present specification at, for example, page 3, line 22; page 9, Example 1, Methods, 2d line; Example 2, 2d paragraph, line 11. This term is clearly supported by the specification as filed, and the objection should be withdrawn.

REJECTION OF THE CLAIMS UNDER 35 USC §112

The Examiner rejected claims 15-20 as lacking written description for the term "infusion".

The rejection is respectfully traversed, and reconsideration is requested.

Applicant directs the Examiner's attention to the present specification at, for example, page 3, line 22; page 9, Example 1, Methods, 2d line; Example 2, 2d paragraph, line 11. This term is clearly supported by the specification as filed, and the rejection should be withdrawn.

REJECTION OF THE CLAIMS UNDER 35 USC §102 (b)

The Examiner rejected claims 15 and 19 as anticipated by Knick et al. which discloses the use of insulin plus metformin for the treatment of 16 type II diabetic patients. The Examiner alleges that insulin is applied as an analogue or derivative of GLP-1 because insulin has a single amino acid in common with GLP-1

The rejection is respectfully traversed, and reconsideration is requested.

The present claims have been amended to call for, and the newly added claims call for, an insulinotropic peptide or an insulinotropic GLP-1 like peptide. An insulinotropic peptide is by definition a peptide that stimulates insulin secretion. Since insulin does not stimulate its own secretion, insulin cannot be considered an insulinotropic peptide.

Accordingly, the rejection of claims 15 and 19 as anticipated by Knick et al. should be withdrawn.

REJECTION OF THE CLAIMS UNDER 35 USC §103(a)

The Examiner rejected claims 15-20 as unpatentable over Buckley et al. (WO 91/11457) and Gutniak et al (Diabetologia, 33 Suppl. A73, Abstract 246, 1990) in view of Ramachandran et al. (Diabete Metabolisme 13(2):140-141, 1987), Del Prato et al (The American Journal of Medicine) and Parker et al. (Diabetes 40:Supp. 1, Abstract 847). The Examiner cites Buckley et al. and Gutniak et al. as disclosing the administration of GLP-1 peptides for the treatment of Type II diabetes. Ramachandran et al. is added as disclosing the oral administration of glibenclamide and metformin in the treatment of Type II diabetes. Del Prato et al. is said to disclose that Type II diabetes appears to be a heterogeneous disorder characterized by insulin deficiency and impaired insulin action. Parker et al. is cited as disclosing that the combination of GLP-1(7-37) and glibenclamide had an additive effect on the amount of insulin secretion. The Examiner concludes that it would have been obvious to administer a GLP-1 like peptide with glibenclamide or metformin.

The rejection is respectfully traversed, and reconsideration is requested.

The Examiner has not demonstrated any reasonable expectation of success in the combination of the cited references that she proposes. It is impossible to predict, with a reasonable expectation of success, what the combined effect of two different drugs will be,

even if the two drugs are used individually to treat the same condition. Combination therapy is not a predictable art. Drug interactions are relatively unpredictable until they are actually studied.

For example, selective serotonin reuptake inhibitors ("SSRIs"), such as Zoloft, and monoamine oxidase inhibitors ("MAOIs") are used to treat the same diseases, including depression. Each is believed to treat depression through a different mechanism. However, it can be fatal to administer an SSRI to someone who is taking an MAOI and the use of the two classes of drugs in combination is contraindicated (See "Warnings" section of 2002 PDR for Zoloft, copy attached). This does not mean that all medications that are used to treat such a disease cannot be used in combination, though. For example, SSRIs are often used with anti-convulsants or atypical anti-psychotics to treat depression. The point is that there is simply no certainty that any combination of drugs will or will not work.

Similarly, the combination of different barbiturates, or the combination of different sedatives, or the combination of different sleeping medications, or the combination of different blood clotting factors, even when each is used individually to treat the same condition, can have adverse and even fatal results, while other combinations of the same types of drugs can have beneficial results.

In diabetics, metformin alone is contraindicated in patients with kidney problems, liver problems, heart failure that is treated with medicines, such as Lanoxin® (digoxin) or Lasix® (furosemide), or in those who drink a lot of alcohol. Many diabetics suffer from these conditions and the effect of combination therapy on such patients would be completely unpredictable.

Finally, the combination of insulin with the oral thiazolinedione drug known as Avandia is also contraindicated for use in treatment of type II diabetes (See last sentence of section entitled "Warnings" in 2002 PDR for Avandia, copy attached). Thus, one cannot always know with reasonable certainty what the effects will be when drugs are used in combination therapy. Only clinical trials can prove which result, harmful or beneficial, will be attained.

The Examiner has really found that it would be obvious to try the presently claimed combination therapy, but this is not the standard of Section 103. There is no evidence that the

success of the presently claimed combination therapy was predictable or that its success was reasonably expected. The combination of an insulinotropic peptide and metformin could have had deleterious effects just as easily as it could have had beneficial effects.

The Examiner's reliance on In re Kerkhoven for the proposition that "it is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose in order to for a third composition to be used for the very same purpose since the idea of combining them flows logically from their having been taught in the prior art" is also misplaced. Kerkhoven concerned a process of producing detergent compositions containing a mixture of known active detergent materials. Adverse drug interactions and contraindications and the health (and possibly life) of a patient are not at issue in formulating a detergent. While the results from mixing and matching detergent components may be anticipated with some degree of success, those from mixing and matching drugs cannot be.

Furthermore, Parker et al. does not disclose that the combination of GLP-1 (7-37) and glibenclamide had an additive effect on the amount of insulin secreted from HIT cells in vivo. Rather, Parker et al. describes experiments conducted on HIT or islet cells in vitro to determine whether or not GLP-1 and glibenclamide operate by the same mechanism or a different mechanism. Parker discloses nothing about combining GLP-1 and glibenclamide in vivo for treating Type II diabetes.

Ramachandran does not disclose that the combination of glibcenclamide and metformin is effective in treatment of type II diabetes. Ramachandran discloses that in 14 NIDDM subjects who showed immunogenic insulin resistance, plasma glucose was successfully controlled in only 6 of those 14 patients. Based on this data, Ramachandran concluded "The present study suggests that a trial of oral hypoglycemic agents may be worthwhile in selected NIDDM patients who show immunogenic insulin resistance" (page 141, emphasis added).

Additionally, none of the cited references suggest substituting metformin for glibenclamide in the Parker combination. Metformin is not chemically or pharmacologically related to any other class of oral hypoglycemic drug (see first paragraph of 2002 PDR for Glucophage, copy attached), so one could not predict that even if the prior art taught that one successfully could use GLP-1 in combination with an SU (which Applicant disputes), that one could also successfully use GLP-1 in combination with metformin.

Moreover, on page 5 of the Office Action, the Examiner suggests that the combination of GLP-1 and glibenclamide would be reasonably expected to be useful in the treatment of type II diabetes because the two agents had an additive effect on insulin secretion. However, as noted in the PDR for Glucophage, with metformin therapy, insulin secretion remains unchanged and fasting insulin levels may actually decrease. Accordingly, the Examiner's rationale for why the combination of GLP-1 and glibenclamide would be effective in treating type II diabetes; i.e., the insulin secretion additive effect, would not apply for GLP-1 and metformin.

The fact that type II diabetes is a heterogenous disorder characterized by relative insulin deficiency and impaired insulin action does not provide a reasonable expectation that a combination therapy as presently claimed would be successful . Type II diabetes is a disease characterized by several different problems with insulin. Furthermore, there are at least six different drug classes for the treatment of type II diabetes including sulfonylureas, glinides, biguanides, insulin, insulin sensitizers ,and alpha-glucosidase inhibitors. Obesity drugs can also be used to treat type 2 diabetics. Newer drugs targets such as glucagon antagonists, DPP-IV (dipeptidyl peptidase-IV) inhibitors; PTPase (protein tyrosine phosphatase) inhibitors; glucokinase activators, inhibitors of hepatic enzymes involved in stimulation of gluconeogenesis and/or glycogenolysis; glucose intake modulators; GSK-3 (glycogen synthase kinase-3) inhibitors; PPARδ activators(peroxisome proliferator-activated receptor) and RXR (retinoid X receptor) agonists, and 11-β-HSD-1 inhibitors are now being investigated. In addition, as noted above, combinations of other well-known drugs such as Avandia and insulin are contraindicated for the treatment of type II diabetes.

All of this directly rebuts the Examiner's reliance on Del Prato as providing a motivation to use the presently claimed combination therapy and as providing a reasonable expectation of success for the claimed combination in the treatment of type II diabetes. Again, the Examiner is actually applying the improper obvious to try standard to Section 103.

Accordingly, in view of the above arguments, Applicant respectfully submits that the combination of insulinotropic peptides and metformin recited in the pending claims is nonobvious over the cited art, and withdrawal of the present rejection is respectfully requested.

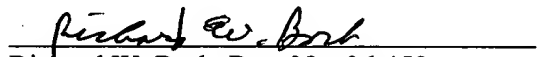
In sum, in view of the above remarks, it is respectfully submitted that all claims are in condition for allowance.

Early action to that end is respectfully requested.

The Examiner is hereby invited to contact the undersigned by telephone if there are any questions concerning this amendment or application.

Respectfully submitted,

Date: June 14, 2004



Richard W. Bork, Reg. No. 36,459
Novo Nordisk Pharmaceuticals, Inc.
100 College Road West
Princeton, NJ 08540
(609) 987-5800

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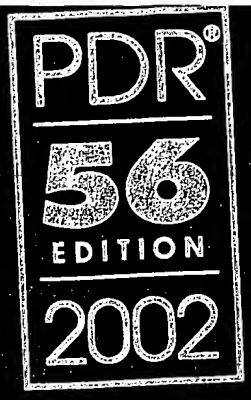

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multiple doses of azithromycin. It has been demonstrated in numerous organ systems (e.g., eye, dorsal root ganglia, liver, gallbladder, kidney, spleen, and pancreas) in rats treated with azithromycin at doses which, expressed on a mg/kg basis, are only 2 times greater than the recommended adult human dose and in rats at doses comparable to the recommended adult human dose. This effect has been reversible after cessation of azithromycin treatment. Phospholipidosis has been observed to a similar extent in the tissues of neonatal rats and dogs given daily doses of azithromycin ranging from 10 days to 30 days. Based on the pharmacokinetic data, phospholipidosis has been seen in the rat (30 mg/kg dose) at observed C_{max} value of 1.3 µg/mL (6 times greater than the observed C_{max} of 0.216 µg/mL at the pediatric dose of 10 mg/kg). Similarly, it has been shown in the dog (10 mg/kg dose) at observed C_{max} value of 1.5 µg/mL (7 times greater than the observed same C_{max} and dose in the studied pediatric population). On mg/m^2 basis, the 30 mg/kg dose in the rat (135 mg/m^2) and 10 mg/kg dose in the dog (79 mg/m^2) are approximately 0.4 and 0.6 times, respectively, the recommended dose in the pediatric patients with an average body weight of 25 kg. This effect, similar to that seen in the adult animals, is reversible after cessation of azithromycin treatment. The significance of these findings for animals and for humans is unknown.

REFERENCES:

1. National Committee for Clinical Laboratory Standards. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically—Third Edition. Approved Standard NCCLS Document M7-A3, Vol. 13, No. 25, NCCLS, Villanova, PA, December, 1993.
2. National Committee for Clinical Laboratory Standards. Performance Standards for Antimicrobial Disk Susceptibility Tests—Fifth Edition. Approved Standard NCCLS Document M2-A5, Vol. 13, No. 24, NCCLS, Villanova, PA, December, 1993.

Pfizer Labs
Division of Pfizer Inc, NY, NY 10017

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Shown in Product Identification Guide, page 332

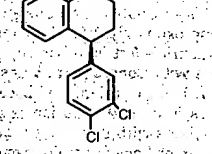
ZOLOFT® ℞

(sertraline hydrochloride)

Tablets and Oral Concentrate

DESCRIPTION

ZOLOFT® (sertraline hydrochloride) is a selective serotonin reuptake inhibitor (SSRI) for oral administration. It is chemically unrelated to other SSRIs, tricyclic, tetracyclic, or other available antidepressant agents. It has a molecular weight of 342.7. Sertraline hydrochloride has the following chemical name: (1S-cis)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-N-methyl-1-naphthalenamine hydrochloride. The empirical formula is $C_{17}H_{17}NCl_2 \cdot HCl$ is represented by the following structural formula:



Sertraline hydrochloride is a white crystalline powder that is slightly soluble in water and isopropyl alcohol, and sparingly soluble in ethanol.

ZOLOFT is supplied for oral administration as scored tablets containing sertraline hydrochloride equivalent to 25, 50 and 100 mg of sertraline and the following inactive ingredients: dibasic calcium phosphate dihydrate, D & C Yellow #10 aluminum lake (in 25 mg tablet), FD & C Blue #1 aluminum lake (in 25 mg tablet), FD & C Red #40 aluminum lake (in 25 mg tablet), FD & C Blue #2 aluminum lake (in 50 mg tablet), hydroxypropyl cellulose, hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polysorbate 80, sodium starch glycolate, synthetic yellow iron oxide (in 100 mg tablet), and titanium dioxide.

ZOLOFT oral concentrate is available in a multidose 60 mL bottle. Each mL of solution contains sertraline hydrochloride equivalent to 20 mg of sertraline. The solution contains the following inactive ingredients: glycerin, alcohol (12%), menthol, butylated hydroxytoluene (BHT). The oral concentrate must be diluted prior to administration (see PRECAUTIONS, Information for Patients and DOSAGE AND ADMINISTRATION).

CLINICAL PHARMACOLOGY

Pharmacodynamics

The mechanism of action of sertraline is presumed to be linked to its inhibition of CNS neuronal uptake of serotonin (5HT). Studies at clinically relevant doses in man have demonstrated that sertraline blocks the uptake of serotonin into human platelets. *In vitro* studies in animals also suggest that sertraline is a potent and selective inhibitor of neuronal serotonin reuptake and has only very weak effects on norepinephrine and dopamine neuronal reuptake. *In vitro* studies have shown that sertraline has no significant affinity for adrenergic ($alpha_1$, $alpha_2$, beta), cholinergic, GABA, dopaminergic, histaminergic, serotonergic ($5HT_{1A}$, $5HT_{1B}$, $5HT_2$), or benzodiazepine receptors; antagonism of such receptors has been hypothesized to be associated with various anticholinergic, sedative, and cardiovascular effects for other psychotropic drugs. The chronic administration of sertraline was found in animals to downregulate brain norepinephrine receptors, as has been observed with other drugs effective in the treatment of major depressive disorder. Sertraline does not inhibit monoamine oxidase.

Pharmacokinetics

Systemic Bioavailability—In man, following oral once-daily dosing over the range of 50 to 200 mg for 14 days, mean peak plasma concentrations (Cmax) of sertraline occurred between 4.5 to 8.4 hours post-dosing. The average terminal elimination half-life of plasma sertraline is about 26 hours. Based on this pharmacokinetic parameter, steady-state sertraline plasma levels should be achieved after approximately one week of once-daily dosing. Linear dose-proportional pharmacokinetics were demonstrated in a single dose study in which the Cmax and area under the plasma concentration time curve (AUC) of sertraline were proportional to dose over a range of 50 to 200 mg. Consistent with the terminal elimination half-life, there is an approximately two-fold accumulation, compared to a single dose, of sertraline with repeated dosing over a 50 to 200 mg dose range. The single dose bioavailability of sertraline tablets is approximately equal to an equivalent dose of solution.

In a relative bioavailability study comparing the pharmacokinetics of 100 mg sertraline as the oral solution to a 100 mg sertraline tablet in 16 healthy adults, the solution to tablet ratio of geometric mean AUC and Cmax values were 114.8% and 120.6%, respectively. 90% confidence intervals (CI) were within the range of 80–125% with the exception of the upper 90% CI limit for Cmax which was 126.5%.

The effects of food on the bioavailability of the sertraline tablet and oral concentrate were studied in subjects administered a single dose with and without food. For the tablet, AUC was slightly increased when drug was administered with food but the Cmax was 25% greater, while the time to reach peak plasma concentration (Tmax) decreased from 8 hours post-dosing to 5.5 hours. For the oral concentrate, Tmax was slightly prolonged from 5.9 hours to 7.0 hours with food.

Metabolism—Sertraline undergoes extensive first pass metabolism. The principal initial pathway of metabolism for sertraline is N-demethylation. N-desmethylsertraline has a plasma terminal elimination half-life of 62 to 104 hours. Both *in vitro* biochemical and *in vivo* pharmacological testing have shown N-desmethylsertraline to be substantially less active than sertraline. Both sertraline and N-desmethylsertraline undergo oxidative deamination and subsequent reduction, hydroxylation, and glucuronide conjugation. In a study of radiolabeled sertraline involving two healthy male subjects, sertraline accounted for less than 5% of the plasma radioactivity. About 40–45% of the administered radioactivity was recovered in urine in 9 days. Unchanged sertraline was not detectable in the urine. For the same period, about 40–45% of the administered radioactivity was accounted for in feces, including 12–14% unchanged sertraline.

Desmethylsertraline exhibits time-related, dose dependent increases in AUC (0–24 hour), Cmax and Cmin, with about a 5–9 fold increase in these pharmacokinetic parameters between day 1 and day 14.

Protein Binding—*In vitro* protein binding studies performed with radiolabeled ^3H-sertraline showed that sertraline is highly bound to serum proteins (98%) in the range of 20 to 500 ng/mL. However, at up to 300 and 200 ng/mL concentrations, respectively, sertraline and N-desmethylsertraline did not alter the plasma protein binding of two other highly protein bound drugs, viz., warfarin and propranolol (see PRECAUTIONS).

Pediatric Pharmacokinetics—Sertraline pharmacokinetics were evaluated in a group of 61 pediatric patients (29 aged 6–12 years, 32 aged 13–17 years) with a DSM-III-R diagnosis of major depressive disorder or obsessive-compulsive disorder. Patients included both males (N=28) and females (N=33). During 42 days of chronic sertraline dosing, sertraline was titrated up to 200 mg/day and maintained at that dose for a minimum of 11 days. On the final day of sertraline 200 mg/day, the 6–12 year old group exhibited a mean sertraline AUC (0–24 hr) of 3107 ng-hr/mL, mean Cmax of 165 ng/mL, and mean half-life of 26.2 hr. The 13–17 year old group exhibited a mean sertraline AUC (0–24 hr) of 2296 ng-hr/mL, mean Cmax of 123 ng/mL, and mean half-life of 27.8 hr. Higher plasma levels in the 6–12 year old group were largely attributable to patients with lower body weights. No gender associated differences were observed. By comparison, a group of 22 separately studied adults between 18 and 45 years of age (11 male, 11 female) received 30 days of 200 mg/day sertraline and exhibited a mean sertraline AUC (0–24 hr) of 2570 ng-hr/mL, mean Cmax of 142 ng/mL, and mean half-life of 27.2 hr. Relative to the adults, both the 6–12 year olds and the 13–17 year olds showed about 22% lower AUC (0–24 hr) and Cmax values when plasma concentration was adjusted for weight. These data suggest that pediatric patients metabolize sertraline with slightly greater efficiency than adults. Nevertheless, lower doses may be advisable for pediatric patients given their lower body weights, especially in very young patients, in order to avoid excessive plasma levels (see DOSAGE AND ADMINISTRATION).

Age—Sertraline plasma clearance in a group of 16 (8 male, 8 female) elderly patients treated for 14 days at a dose of 100 mg/day was approximately 40% lower than in a similarly studied group of younger (25 to 32 y.o.) individua

Steady-state, therefore, should be achieved after 2 to weeks in older patients. The same study showed a c creased clearance of desmethylsertraline in older males, b not in older females.

Liver Disease—As might be predicted from its primary s of metabolism, liver impairment can affect the eliminati of sertraline. In patients with chronic mild liver impairme (N=10, 8 patients with Child-Pugh scores of 5–6 and 2 p tients with Child-Pugh scores of 7–8) who received 50 r sertraline per day maintained for 21 days, sertraline cle ance was reduced, resulting in approximately 3-fold great exposure compared to age-matched volunteers with no h patic impairment (N=10). The exposure to desmethylsertr line was approximately 2-fold greater compared to ag matched volunteers with no hepatic impairment. The were no significant differences in plasma protein binding c served between the two groups. The effects of sertraline patients with moderate and severe hepatic impairme have not been studied. The results suggest that the use sertraline in patients with liver disease must be approach with caution. If sertraline is administered to patients wi liver impairment, a lower or less frequent dose should used (see PRECAUTIONS and DOSAGE AND ADMINI TRATION).

Renal Disease—Sertraline is extensively metabolized a excretion of unchanged drug in urine is a minor route elimination. In volunteers with mild to modera (CLcr=30–60 mL/min), moderate to severe (CLcr=10– mL/min) or severe (receiving hemodialysis) renal impa ment (N=10 each group), the pharmacokinetics and prote binding of 200 mg sertraline per day maintained for 21 da were not altered compared to age-matched voluntee (N=12) with no renal impairment. Thus sertraline multip dose pharmacokinetics appear to be unaffected by renal i pairment (see PRECAUTIONS).

Clinical Trials

Major Depressive Disorder—The efficacy of ZOLOFT as treatment for major depressive disorder was established two placebo-controlled studies in adult outpatients meetin DSM-III criteria for major depressive disorder. Study 1 w an 8-week study with flexible dosing of ZOLOFT in a ran of 50 to 200 mg/day; the mean dose for completers was 1 mg/day. Study 2 was a 6-week fixed-dose study, includi ZOLOFT doses of 50, 100, and 200 mg/day. Overall, the studies demonstrated ZOLOFT to be superior to placebo the Hamilton Depression Rating Scale and the Clinic Global Impression Severity and Improvement scales. Stu 2 was not readily interpretable regarding a dose respon relationship for effectiveness.

Study 3 involved depressed outpatients who had respond by the end of an initial 8-week open treatment phase ZOLOFT 50–200 mg/day. These patients (N=295) were ra domized to continuation for 44 weeks on double-bli ZOLOFT 50–200 mg/day or placebo. A statistically signi cantly lower relapse rate was observed for patients taki ZOLOFT compared to those on placebo. The mean dose f completers was 70 mg/day.

Analyses for gender effects on outcome did not suggest a differential responsiveness on the basis of sex.

Obsessive-Compulsive Disorder (OCD)—The effectivene of ZOLOFT in the treatment of OCD was demonstrated three multicenter placebo-controlled studies of adult outp tients (Studies 1–3). Patients in all studies had moderate severe OCD (DSM-III or DSM-III-R) with mean baseli ratings on the Yale Brown Obsessive-Compulsive Sca (YBOCS) total score ranging from 23 to 25.

Study 1 was an 8-week study with flexible dosing ZOLOFT in a range of 50 to 200 mg/day; the mean dose f completers was 186 mg/day. Patients receiving ZOLOFT e perienced a mean reduction of approximately 4 points the YBOCS total score which was significantly greater tha the mean reduction of 2 points in placebo-treated patient

Study 2 was a 12-week fixed-dose study, including ZOLOF doses of 50, 100, and 200 mg/day. Patients receivin ZOLOFT doses of 50 and 200 mg/day experienced mean r ductions of approximately 6 points on the YBOCS tot score which were significantly greater than the approx mately 3 point reduction in placebo-treated patients.

Study 3 was a 12-week study with flexible dosing ZOLOFT in a range of 50 to 200 mg/day; the mean dose f completers was 185 mg/day. Patients receiving ZOLOFT e perienced a mean reduction of approximately 7 points the YBOCS total score which was significantly greater tha the mean reduction of approximately 4 points in placeb treated patients.

Analyses for age and gender effects on outcome did not su gest any differential responsiveness on the basis of age sex.

The effectiveness of ZOLOFT for the treatment of OCD wa also demonstrated in a 12-week, multicenter, parallel grou study in a pediatric outpatient population (children an adolescents, ages 6–17). Patients in this study were init ated at doses of either 25 mg/day (children, ages 6–12) or 5 mg/day (adolescents, ages 13–17), and then titrated over th next four weeks to a maximum dose of 200 mg/day, as to erated. The mean dose for completers was 178 mg/day. Dos ing was once a day in the morning or evening. Patients i this study had moderate to severe OCD (DSM-III-R) wit mean baseline ratings on the Children's Yale-Brown Obse sive-Compulsive Scale (CYBOCS) total score of 22. Patient receiving sertraline experienced a mean reduction of ap proximately 7 units on the CYBOCS total score which wa significantly greater than the 3 unit reduction for placeb

Continued on next page

patients. Analyses for age and gender effects on outcome did not suggest any differential responsiveness on the basis of age or sex.

Panic Disorder—The effectiveness of ZOLOFT in the treatment of panic disorder was demonstrated in three double-blind, placebo-controlled studies (Studies 1–3) of adult outpatients who had a primary diagnosis of panic disorder (DSM-III-R), with or without agoraphobia.

Studies 1 and 2 were 10-week flexible dose studies. ZOLOFT was initiated at 25 mg/day for the first week, and then patients were dosed in a range of 50–200 mg/day on the basis of clinical response and toleration. The mean ZOLOFT doses for completers to 10 weeks were 131 mg/day and 144 mg/day, respectively, for Studies 1 and 2. In these studies, ZOLOFT was shown to be significantly more effective than placebo on change from baseline in panic attack frequency and on the Clinical Global Impression Severity of Illness and Global Improvement scores. The difference between ZOLOFT and placebo in reduction from baseline in the number of full panic attacks was approximately 2 panic attacks per week in both studies.

Study 3 was a 12-week fixed-dose study, including ZOLOFT doses of 50, 100, and 200 mg/day. Patients receiving ZOLOFT experienced a significantly greater reduction in panic attack frequency than patients receiving placebo. Study 3 was not readily interpretable regarding a dose response relationship for effectiveness.

Subgroup analyses did not indicate that there were any differences in treatment outcomes as a function of age, race, or gender.

Posttraumatic Stress Disorder (PTSD)—The effectiveness of ZOLOFT in the treatment of PTSD was established in two multicenter placebo-controlled studies (Studies 1–2) of adult outpatients who met DSM-III-R criteria for PTSD. The mean duration of PTSD for these patients was 12 years (Studies 1 and 2 combined) and 44% of patients (169 of the 385 patients treated) had secondary depressive disorder.

Studies 1 and 2 were 12-week flexible dose studies. ZOLOFT was initiated at 25 mg/day for the first week, and patients were then dosed in the range of 50–200 mg/day on the basis of clinical response and toleration. The mean ZOLOFT dose for completers was 146 mg/day and 151 mg/day, respectively for Studies 1 and 2. Study outcome was assessed by the Clinician-Administered PTSD Scale Part 2 (CAPS) which is a multi-item instrument that measures the three PTSD diagnostic symptom clusters of reexperiencing/intrusion, avoidance/numbing, and hyperarousal as well as the patient-rated Impact of Event Scale (IES) which measures intrusion and avoidance symptoms. ZOLOFT was shown to be significantly more effective than placebo on change from baseline to endpoint on the CAPS, IES and on the Clinical Global Impressions (CGI) Severity of Illness and Global Improvement scores. In two additional placebo-controlled PTSD trials, the difference in response to treatment between patients receiving ZOLOFT and patients receiving placebo was not statistically significant. One of these additional studies was conducted in patients similar to those recruited for Studies 1 and 2, while the second additional study was conducted in predominantly male veterans.

PTSD is a more common disorder in women than men, the majority (76%) of patients in these trials were women (152 and 139 women on sertraline and placebo versus 39 and 55 men on sertraline and placebo; Studies 1 and 2 combined). Post hoc exploratory analyses revealed a significant difference between ZOLOFT and placebo on the CAPS, IES and CGI in women, regardless of baseline diagnosis of comorbid major depressive disorder, but essentially no effect in the relatively smaller number of men in these studies. The clinical significance of this apparent gender interaction is unknown at this time. There was insufficient information to determine the effect of race or age on outcome.

In a longer-term study, patients meeting DSM-III-R criteria for PTSD who had responded during a 24-week open trial on ZOLOFT 50–200 mg/day (n=96) were randomized to continuation of ZOLOFT or to substitution of placebo for up to 28 weeks of observation for relapse. Response during the open phase was defined as a CGI-I of 1 (very much improved) or 2 (much improved), and a decrease in the CAPS-2 score of 30% compared to baseline. Relapse during the double-blind phase was defined as the following conditions being met on two consecutive visits: (1) CGI-I ≥3; (2) CAPS-2 score increased by ≥30% and by ≥15 points relative to baseline; and (3) worsening of the patient's condition in the investigator's judgment. Patients receiving continued ZOLOFT treatment experienced significantly lower relapse rates over the subsequent 28 weeks compared to those receiving placebo. This pattern was demonstrated in male and female subjects.

INDICATIONS AND USAGE

Major Depressive Disorder—ZOLOFT® (sertraline hydrochloride) is indicated for the treatment of major depressive disorder.

The efficacy of ZOLOFT in the treatment of a major depressive episode was established in six to eight week controlled trials of outpatients whose diagnoses corresponded most closely to the DSM-III category of major depressive disorder (see Clinical Trials under CLINICAL PHARMACOLOGY).

A major depressive episode implies a prominent and relatively persistent depressed or dysphoric mood that usually interferes with daily functioning (nearly every day for at least 2 weeks); it should include at least 4 of the following 8 symptoms: change in appetite, change in sleep, psychomotor agitation or retardation, loss of interest in usual activities or decrease in sexual drive, increased fatigue, feelings of guilt or worthlessness, slowed thinking or impaired concentration, and a suicide attempt or suicidal ideation.

The antidepressant action of ZOLOFT in hospitalized depressed patients has not been adequately studied.

The efficacy of ZOLOFT in maintaining an antidepressant response for up to 44 weeks following 8 weeks of open-label acute treatment (52 weeks total) was demonstrated in a placebo-controlled trial. The usefulness of the drug in patients receiving ZOLOFT for extended periods should be reevaluated periodically (see Clinical Trials under CLINICAL PHARMACOLOGY).

Obsessive-Compulsive Disorder—ZOLOFT is indicated for the treatment of obsessions and compulsions in patients with obsessive-compulsive disorder (OCD), as defined in the DSM-III-R; i.e., the obsessions or compulsions cause marked distress, are time-consuming, or significantly interfere with social or occupational functioning.

The efficacy of ZOLOFT was established in 12-week trials with obsessive-compulsive outpatients having diagnoses of obsessive-compulsive disorder as defined according to DSM-III or DSM-III-R criteria (see Clinical Trials under CLINICAL PHARMACOLOGY).

Obsessive-compulsive disorder is characterized by recurrent and persistent ideas, thoughts, impulses, or images (obsessions) that are ego-dystonic and/or repetitive, purposeful, and intentional behaviors (compulsions) that are recognized by the person as excessive or unreasonable.

The effectiveness of ZOLOFT in long-term use for OCD, i.e., for more than 12 weeks, has not been systematically evaluated in placebo-controlled trials. Therefore, the physician who elects to use ZOLOFT for extended periods should periodically reevaluate the long-term usefulness of the drug for the individual patient (see DOSAGE AND ADMINISTRATION).

Panic Disorder—ZOLOFT is indicated for the treatment of panic disorder, with or without agoraphobia, as defined in DSM-IV. Panic disorder is characterized by the occurrence of unexpected panic attacks and associated concern about having additional attacks, worry about the implications or consequences of the attacks, and/or a significant change in behavior related to the attacks.

The efficacy of ZOLOFT was established in three 10–12 week trials in panic disorder patients whose diagnoses corresponded to the DSM-III-R category of panic disorder (see Clinical Trials under CLINICAL PHARMACOLOGY).

Panic disorder (DSM-IV) is characterized by recurrent unexpected panic attacks, i.e., a discrete period of intense fear or discomfort in which four (or more) of the following symptoms develop abruptly and reach a peak within 10 minutes: (1) palpitations, pounding heart, or accelerated heart rate; (2) sweating; (3) trembling or shaking; (4) sensations of shortness of breath or smothering; (5) feeling of choking; (6) chest pain or discomfort; (7) nausea or abdominal distress; (8) feeling dizzy, unsteady, lightheaded, or faint; (9) derealization (feelings of unreality) or depersonalization (being detached from oneself); (10) fear of losing control; (11) fear of dying; (12) paresthesias (numbness or tingling sensations); (13) chills or hot flushes.

The effectiveness of ZOLOFT® (sertraline hydrochloride) in long-term use, that is, for more than 12 weeks, has not been systematically evaluated in controlled trials. Therefore, the physician who elects to use ZOLOFT for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient (see DOSAGE AND ADMINISTRATION).

Posttraumatic Stress Disorder (PTSD)—ZOLOFT (sertraline hydrochloride) is indicated for the treatment of posttraumatic stress disorder.

The efficacy of ZOLOFT in the treatment of PTSD was established in two 12-week placebo-controlled trials of outpatients whose diagnosis met criteria for the DSM-III-R category of PTSD (see Clinical Trials under CLINICAL PHARMACOLOGY).

PTSD, as defined by DSM-III-R/IV, requires exposure to a traumatic event that involved actual or threatened death or serious injury, or threat to the physical integrity of self or others, and a response which involves intense fear, helplessness, or horror. Symptoms that occur as a result of exposure to the traumatic event include reexperiencing of the event in the form of intrusive thoughts, flashbacks or dreams, and intense psychological distress and physiological reactivity on exposure to cues to the event; avoidance of situations reminiscent of the traumatic event, inability to recall details of the event, and/or numbing of general responsiveness manifested as diminished interest in significant activities, estrangement from others, restricted range of affect, or sense of foreshortened future; and symptoms of autonomic arousal including hypervigilance, exaggerated startle response, sleep disturbance, impaired concentration, and irritability or outbursts of anger. A PTSD diagnosis requires that the symptoms are present for at least a month and that they cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

The efficacy of ZOLOFT in maintaining a response in patients with PTSD for up to 28 weeks following 24 weeks of open-label treatment was demonstrated in a placebo-controlled trial. Nevertheless, the physician who elects to use ZOLOFT for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient (see Clinical Trials under CLINICAL PHARMACOLOGY).

CONTRAINDICATIONS

All Dosage Forms of ZOLOFT:

Concomitant use in patients taking monoamine oxidase inhibitors (MAOIs) is contraindicated (see WARNINGS).

Oral Concentrate:

ZOLOFT oral concentrate is contraindicated in patients taking ANTABUSE (disulfiram) due to the alcohol content in the concentrate.

WARNINGS

Cases of serious sometimes fatal reactions have been reported in patients receiving ZOLOFT® (sertraline hydrochloride), a selective serotonin reuptake inhibitor (SSRI), in combination with a monoamine oxidase inhibitor (MAOI). Symptoms of a drug interaction between an SSRI and an MAOI include: hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, mental status changes that include confusion, irritability, and extreme agitation progressing to delirium and coma. These reactions have also been reported in patients who have recently discontinued an SSRI and have been started on an MAOI. Some cases presented with features resembling neuroleptic malignant syndrome. Therefore, ZOLOFT should not be used in combination with an MAOI, or within 14 days of discontinuing treatment with an MAOI. Similarly, at least 14 days should be allowed after stopping ZOLOFT before starting an MAOI.

PRECAUTIONS

General

Activation of Mania/Hypomania—During premarket testing, hypomania or mania occurred in approximately 0.4% of ZOLOFT® (sertraline hydrochloride) treated patients.

Weight Loss—Significant weight loss may be an undesirable result of treatment with sertraline for some patients, but on average, patients in controlled trials had minimal (1 to 2 pound weight loss, versus smaller changes on placebo. Only rarely have sertraline patients been discontinued for weight loss.

Seizure—ZOLOFT has not been evaluated in patients with a seizure disorder. These patients were excluded from clinical studies during the product's premarket testing. No seizures were observed among approximately 3000 patients treated with ZOLOFT in the development program for major depressive disorder. However, 4 patients out of approximately 1800 (220<18 years of age) exposed during the development program for obsessive-compulsive disorder experienced seizures, representing a crude incidence of 0.2%. Three of these patients were adolescents, two with a seizure disorder and one with a family history of seizure disorder, none of whom were receiving anticonvulsant medication. Accordingly, ZOLOFT should be introduced with care in patients with a seizure disorder.

Suicide—The possibility of a suicide attempt is inherent in major depressive disorder and may persist until significant remission occurs. Close supervision of high risk patients should accompany initial drug therapy. Prescriptions for ZOLOFT should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose.

Because of the well-established comorbidity between OCD and major depressive disorder, panic disorder and major depressive disorder, and PTSD and major depressive disorder, the same precautions observed when treating patients with major depressive disorder should be observed when treating patients with OCD, panic disorder or PTSD.

Weak Uricosuric Effect—ZOLOFT® (sertraline hydrochloride) is associated with a mean decrease in serum uric acid of approximately 7%. The clinical significance of this weak uricosuric effect is unknown.

Use in Patients with Concomitant Illness—Clinical experience with ZOLOFT in patients with certain concomitant systemic illness is limited. Caution is advisable in using ZOLOFT in patients with diseases or conditions that could affect metabolism or hemodynamic responses.

ZOLOFT has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were excluded from clinical studies during the product's premarket testing. However, the electrocardiograms of 774 patients who received ZOLOFT in double-blind trials were evaluated and the data indicate that ZOLOFT is not associated with the development of significant ECG abnormalities.

ZOLOFT is extensively metabolized by the liver. In patients with chronic mild liver impairment, sertraline clearance was reduced, resulting in increased AUC, Cmax and elimination half-life. The effects of sertraline in patients with moderate and severe hepatic impairment have not been studied. The use of sertraline in patients with liver disease must be approached with caution. If sertraline is administered to patients with liver impairment, a lower or less frequent dose should be used (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION).

Since ZOLOFT is extensively metabolized, excretion of unchanged drug in urine is a minor route of elimination. A clinical study comparing sertraline pharmacokinetics in healthy volunteers to that in patients with renal impairment ranging from mild to severe (requiring dialysis) indicated that the pharmacokinetics and protein binding are unaffected by renal disease. Based on the pharmacokinetic results, there is no need for dosage adjustment in patients with renal impairment (see CLINICAL PHARMACOLOGY).

Interference with Cognitive and Motor Performance—In controlled studies, ZOLOFT did not cause sedation and did not interfere with psychomotor performance. (See Information for Patients.)

natremia—Several cases of hyponatremia have been reported and appeared to be reversible when ZOLOFT was discontinued. Some cases were possibly due to the syndrome of inappropriate antidiuretic hormone secretion. The majority of these occurrences have been in elderly individuals, and in patients taking diuretics or who were otherwise volume depleted.

Platelet Function—There have been rare reports of altered platelet function and/or abnormal results from laboratory studies in patients taking ZOLOFT. While there have been reports of abnormal bleeding or purpura in several patients using ZOLOFT, it is unclear whether ZOLOFT had a causative role.

Information for Patients

Physicians are advised to discuss the following issues with patients for whom they prescribe ZOLOFT:

Patients should be told that although ZOLOFT has not been shown to impair the ability of normal subjects to perform tasks requiring complex motor and mental skills in laboratory experiments, drugs that act upon the central nervous system may affect some individuals adversely. Therefore, patients should be told that until they learn how they respond to ZOLOFT they should be careful doing activities when they need to be alert, such as driving a car or operating machinery.

Patients should be told that although ZOLOFT has not been shown in experiments with normal subjects to increase the mental and motor skill impairments caused by alcohol, the concomitant use of ZOLOFT and alcohol is not advised.

Patients should be told that while no adverse interaction of ZOLOFT with over-the-counter (OTC) drug products is known to occur, the potential for interaction exists. Thus, the use of any OTC product should be initiated cautiously according to the directions of use given for the OTC product.

Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy with ZOLOFT.

Patients should be advised to notify their physician if they are breast feeding an infant.

ZOLOFT oral concentrate is contraindicated with ANTABUSE (disulfiram) due to the alcohol content of the concentrate.

ZOLOFT Oral Concentrate contains 20 mg/mL of sertraline (as the hydrochloride) as the active ingredient and 12% alcohol. ZOLOFT Oral Concentrate must be diluted before use. Just before taking, use the dropper provided to remove the required amount of ZOLOFT Oral Concentrate and mix with 4 oz (1/2 cup) of water, ginger ale, lemon/lime soda, lemonade or orange juice ONLY. Do not mix ZOLOFT Oral Concentrate with anything other than the liquids listed. The dose should be taken immediately after mixing. Do not mix in advance. At times, a slight haze may appear after mixing; this is normal. Note that caution should be exercised for persons with latex sensitivity, as the dropper dispenser contains dry natural rubber.

Laboratory Tests

None.

Drug Interactions

Potential Effects of Coadministration of Drugs Highly Bound to Plasma Proteins—Because sertraline is tightly bound to plasma protein, the administration of ZOLOFT® (sertraline hydrochloride) to a patient taking another drug which is tightly bound to protein (e.g., warfarin, digitoxin) may cause a shift in plasma concentrations potentially resulting in an adverse effect. Conversely, adverse effects may result from displacement of protein bound ZOLOFT by other tightly bound drugs.

In a study comparing prothrombin time AUC (0–120 hr) following dosing with warfarin (0.75 mg/kg) before and after 21 days of dosing with either ZOLOFT (50–200 mg/day) or placebo, there was a mean increase in prothrombin time of 1% relative to baseline for ZOLOFT compared to a 1% decrease for placebo ($p<0.02$). The normalization of prothrombin time for the ZOLOFT group was delayed compared to the placebo group. The clinical significance of this change is unknown. Accordingly, prothrombin time should be carefully monitored when ZOLOFT therapy is initiated or stopped.

Cimetidine—In a study assessing disposition of ZOLOFT 100 mg on the second of 8 days of cimetidine administration (800 mg daily), there were significant increases in ZOLOFT mean AUC (50%), Cmax (24%) and half-life (26%) compared to the placebo group. The clinical significance of these changes is unknown.

CNS Active Drugs—In a study comparing the disposition of intravenously administered diazepam before and after 21 days of dosing with either ZOLOFT (50 to 200 mg/day escalating dose) or placebo, there was a 32% decrease relative to baseline in diazepam clearance for the ZOLOFT group compared to a 19% decrease relative to baseline for the placebo group ($p<0.03$). There was a 23% increase in Tmax for desmethyldiazepam in the ZOLOFT group compared to a 20% decrease in the placebo group ($p<0.03$). The clinical significance of these changes is unknown.

In a placebo-controlled trial in normal volunteers, the administration of two doses of ZOLOFT did not significantly affect steady-state lithium levels or the renal clearance of lithium. Nevertheless, at this time, it is recommended that plasma lithium levels be monitored following initiation of ZOLOFT therapy with appropriate adjustments to the lithium dose. The risk of using ZOLOFT in combination with other CNS active drugs has not been systematically evaluated. Consequently, caution is advised if the concomitant administration of ZOLOFT and such drugs is required.

MOST COMMON TREATMENT-EMERGENT ADVERSE EVENTS: INCIDENCE IN PLACEBO-CONTROLLED CLINICAL TRIALS

	Percentage of Patients Reporting Event							
	Major Depressive Disorder/Other*		OCD		Panic Disorder		PTSD	
Body System/ Adverse Event	ZOLOFT (N=861)	Placebo (N=853)	ZOLOFT (N=533)	Placebo (N=373)	ZOLOFT (N=430)	Placebo (N=275)	ZOLOFT (N=374)	Placebo (N=376)
Autonomic Nervous System Disorders								
Ejaculation Failure[1]	7	<1	17	2	19	1	11	1
Mouth Dry	16	9	14	9	15	10	11	6
Sweating Increased	8	3	6	1	5	1	4	2
Centr. & Periph. Nerv. System Disorders								
Somnolence	13	6	15	8	15	9	13	9
Tremor	11	3	8	1	5	1	5	1
General								
Fatigue	11	8	14	10	11	6	10	5
Gastrointestinal Disorders								
Anorexia	3	2	11	2	7	2	8	2
Constipation	8	6	6	4	7	3	3	3
Diarrhea/Loose Stools	18	9	24	10	20	9	24	15
Dyspepsia	6	3	10	4	10	8	6	6
Nausea	26	12	30	11	29	18	21	11
Psychiatric Disorders								
Agitation	6	4	6	3	6	2	5	5
Insomnia	16	9	28	12	25	18	20	11
Libido Decreased	1	<1	11	2	7	1	7	2

[1]Primarily ejaculatory delay. Denominator used was for male patients only (N=271 ZOLOFT major depressive disorder/other*; N=271 placebo major depressive disorder/other*; N=296 ZOLOFT OCD; N=219 placebo OCD; N=216 ZOLOFT panic disorder; N=134 placebo panic disorder; N=130 ZOLOFT PTSD; N=149 placebo PTSD).
*Major depressive disorder and other premarketing controlled trials.

There is limited controlled experience regarding the optimal timing of switching from other drugs effective in the treatment of major depressive disorder, obsessive-compulsive disorder, panic disorder, and posttraumatic stress disorder to ZOLOFT. Care and prudent medical judgment should be exercised when switching, particularly from long-acting agents. The duration of an appropriate washout period which should intervene before switching from one selective serotonin reuptake inhibitor (SSRI) to another has not been established.

Monoamine Oxidase Inhibitors—See CONTRAINDICATIONS and WARNINGS.

Drugs Metabolized by P450 3A4—In two separate *in vivo* interaction studies, sertraline was co-administered with cytochrome P450 3A4-substrates, terfenadine or carbamazepine, under steady-state conditions. The results of these studies demonstrated that sertraline co-administration did not increase plasma concentrations of terfenadine or carbamazepine. These data suggest that sertraline's extent of inhibition of P450 3A4 activity is not likely to be of clinical significance.

Drugs Metabolized by P450 2D6—Many drugs effective in the treatment of major depressive disorder, e.g., the SSRIs, including sertraline, and most tricyclic antidepressant drugs effective in the treatment of major depressive disorder inhibit the biochemical activity of the drug metabolizing isozyme cytochrome P450 2D6 (debrisoquin hydroxylase), and, thus, may increase the plasma concentrations of co-administered drugs that are metabolized by P450 2D6. The drugs for which this potential interaction is of greatest concern are those metabolized primarily by 2D6 and which have a narrow therapeutic index, e.g., the tricyclic antidepressant drugs effective in the treatment of major depressive disorder and the Type 1C antiarrhythmics propafenone and flecainide. The extent to which this interaction is an important clinical problem depends on the extent of the inhibition of P450 2D6 by the antidepressant and the therapeutic index of the co-administered drug. There is variability among the drugs effective in the treatment of major depressive disorder in the extent of clinically important 2D6 inhibition, and in fact sertraline at lower doses has a less prominent inhibitory effect on 2D6 than some others in the class. Nevertheless, even sertraline has the potential for clinically important 2D6 inhibition. Consequently, concomitant use of a drug metabolized by P450 2D6 with ZOLOFT may require lower doses than usually prescribed for the other drug. Furthermore, whenever ZOLOFT is withdrawn from co-therapy, an increased dose of the co-administered drug may be required (see Tricyclic Antidepressant Drugs Effective in the Treatment of Major Depressive Disorder under PRECAUTIONS).

Sumatriptan—There have been rare postmarketing reports describing patients with weakness, hyperreflexia, and incoordination following the use of a selective serotonin reuptake inhibitor (SSRI) and sumatriptan. If concomitant treatment with sumatriptan and an SSRI (e.g., citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline) is clinically warranted, appropriate observation of the patient is advised.

Tricyclic Antidepressant Drugs Effective in the Treatment of Major Depressive Disorder (TCAs)—The extent to which SSRI-TCA interactions may pose clinical problems will depend on the degree of inhibition and the pharmacokinetics of the SSRI involved. Nevertheless, caution is indicated in the co-administration of TCAs with ZOLOFT, because sertraline may inhibit TCA metabolism. Plasma TCA concentrations may need to be monitored, and the dose of TCA may need to be reduced, if a TCA is co-administered with ZOLOFT (see Drugs Metabolized by P450 2D6 under PRECAUTIONS).

Hypoglycemic Drugs—In a placebo-controlled trial in normal volunteers, administration of ZOLOFT for 22 days (including 200 mg/day for the final 13 days) caused a statistically significant 16% decrease from baseline in the clearance of tolbutamide following an intravenous 1000 mg dose. ZOLOFT administration did not noticeably change either the plasma protein binding or the apparent volume of distribution of tolbutamide, suggesting that the decreased clearance was due to a change in the metabolism of the drug. The clinical significance of this decrease in tolbutamide clearance is unknown.

Atenolol—ZOLOFT (100 mg) when administered to 10 healthy male subjects had no effect on the beta-adrenergic blocking ability of atenolol.

Digoxin—In a placebo-controlled trial in normal volunteers, administration of ZOLOFT for 17 days (including 200 mg/day for the last 10 days) did not change serum digoxin levels or digoxin renal clearance.

Microsomal Enzyme Induction—Preclinical studies have shown ZOLOFT to induce hepatic microsomal enzymes. In

Continued on next page

clinical studies, ZOLOFT was shown to induce hepatic enzymes minimally as determined by a small (5%) but statistically significant decrease in antipyrine half-life following administration of 200 mg/day for 21 days. This small change in antipyrine half-life reflects a clinically insignificant change in hepatic metabolism.

Electroconvulsive Therapy—There are no clinical studies establishing the risks or benefits of the combined use of electroconvulsive therapy (ECT) and ZOLOFT.

Alcohol—Although ZOLOFT did not potentiate the cognitive and psychomotor effects of alcohol in experiments with normal subjects, the concomitant use of ZOLOFT and alcohol is not recommended.

Carcinogenesis—Lifetime carcinogenicity studies were carried out in CD-1 mice and Long-Evans rats at doses up to 40 mg/kg/day. These doses correspond to 1 times (mice) and 2 times (rats) the maximum recommended human dose (MRHD) on a mg/m^2 basis. There was a dose-related increase of liver adenomas in male mice receiving sertraline at 10–40 mg/kg (0.25–1.0 times the MRHD on a mg/m^2 basis). No increase was seen in female mice or in rats of either sex receiving the same treatments, nor was there an increase in hepatocellular carcinomas. Liver adenomas have a variable rate of spontaneous occurrence in the CD-1 mouse and are of unknown significance to humans. There was an increase in follicular adenomas of the thyroid in female rats receiving sertraline at 40 mg/kg (2 times the MRHD on a mg/m^2 basis); this was not accompanied by thyroid hyperplasia. While there was an increase in uterine adenocarcinomas in rats receiving sertraline at 10–40 mg/kg (0.5–2.0 times the MRHD on a mg/m^2 basis) compared to placebo controls, this effect was not clearly drug related.

Mutagenesis—Sertraline had no genotoxic effects, with or without metabolic activation, based on the following assays: bacterial mutation assay; mouse lymphoma mutation assay; and tests for cytogenetic aberrations *in vivo* in mouse bone marrow and *in vitro* in human lymphocytes.

Impairment of Fertility—A decrease in fertility was seen in one of two rat studies at a dose of 80 mg/kg (4 times the maximum recommended human dose on a mg/m^2 basis).

Pregnancy—Pregnancy Category C—Reproduction studies have been performed in rats and rabbits at doses up to 80 mg/kg/day and 40 mg/kg/day, respectively. These doses correspond to approximately 4 times the maximum recommended human dose (MRHD) on a mg/m^2 basis. There was no evidence of teratogenicity at any dose level. When pregnant rats and rabbits were given sertraline during the period of organogenesis, delayed ossification was observed in fetuses at doses of 10 mg/kg (0.5 times the MRHD on a mg/m^2 basis) in rats and 40 mg/kg (4 times the MRHD on a mg/m^2 basis) in rabbits. When female rats received sertraline during the last third of gestation and throughout lactation, there was an increase in the number of stillborn pups and in the number of pups dying during the first 4 days after birth. Pup body weights were also decreased during the first four days after birth. These effects occurred at a dose of 20 mg/kg (1 times the MRHD on a mg/m^2 basis). The no effect dose for rat pup mortality was 10 mg/kg (0.5 times the MRHD on a mg/m^2 basis). The decrease in pup survival was shown to be due to *in utero* exposure to sertraline. The clinical significance of these effects is unknown. There are no adequate and well-controlled studies in pregnant women. ZOLOFT® (sertraline hydrochloride) should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery—The effect of ZOLOFT on labor and delivery in humans is unknown.

Nursing Mothers—It is not known whether, and if so in what amount, sertraline or its metabolites are excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when ZOLOFT is administered to a nursing woman.

Pediatric Use—The efficacy of ZOLOFT for the treatment of obsessive-compulsive disorder was demonstrated in a 12-week, multicenter, placebo-controlled study with 187 outpatients ages 6–17 (see Clinical Trials under CLINICAL PHARMACOLOGY). The effectiveness of ZOLOFT in pediatric patients with major depressive disorder or panic disorder has not been systematically evaluated.

Sertraline pharmacokinetics were evaluated in 61 pediatric patients between 6 and 17 years of age with major depressive disorder or OCD and revealed similar drug exposures to those of adults when plasma concentration was adjusted for weight (see Pharmacokinetics under CLINICAL PHARMACOLOGY).

More than 250 patients with major depressive disorder or OCD between 6 and 17 years of age have received ZOLOFT in clinical trials. The adverse event profile observed in these patients was generally similar to that observed in adult studies with ZOLOFT (see ADVERSE REACTIONS). As with other SSRIs, decreased appetite and weight loss have been observed in association with the use of ZOLOFT. Consequently, regular monitoring of weight and growth is recommended if treatment of a child with an SSRI is to be continued long term. Safety and effectiveness in pediatric patients below the age of 6 have not been established.

The risks, if any, that may be associated with sertraline's extended use in children and adolescents with OCD have not been systematically assessed. The prescriber should be mindful that the evidence relied upon to conclude that sertraline is safe for use in children and adolescents derives from relatively short-term clinical studies and from extrapolation of experience gained with adult patients. In particular, there are no studies that directly evaluate the effects of long-term sertraline use on the growth, development, and maturation of children and adolescents. Although there is no affirmative finding to suggest that sertraline possesses a capacity to adversely affect growth, development or maturation, the absence of such findings is not compelling evidence of the absence of the potential of sertraline to have adverse effects in chronic use.

Geriatric Use—U.S. geriatric clinical studies of ZOLOFT in major depressive disorder included 663 ZOLOFT-treated subjects ≥ 65 years of age, of those, 180 were ≥ 75 years of age. No overall differences in the pattern of adverse reactions were observed in the geriatric clinical trial subjects relative to those reported in younger subjects (see ADVERSE REACTIONS), and other reported experience has not identified differences in safety patterns between the elderly and younger subjects. As with all medications, greater sensitivity of some older individuals cannot be ruled out. There were 947 subjects in placebo-controlled geriatric clinical studies of ZOLOFT in major depressive disorder. No overall differences in the pattern of efficacy were observed in the geriatric clinical trial subjects relative to those reported in younger subjects.

Other Adverse Events in Geriatric Patients. In 354 geriatric subjects treated with ZOLOFT in placebo-controlled trials, the overall profile of adverse events was generally similar to that shown in Tables 1 and 2. Urinary tract infection was the only adverse event not appearing in Tables 1 and 2 and reported at an incidence of at least 2% and at a rate greater than placebo in placebo-controlled trials.

As with other SSRIs, ZOLOFT has been associated with cases of clinically significant hyponatremia in elderly patients (see Hyponatremia under PRECAUTIONS).

TABLE 2
TREATMENT-EMERGENT ADVERSE EVENTS: INCIDENCE IN PLACEBO-CONTROLLED CLINICAL TRIALS
Percentage of Patients Reporting Event
Major Depressive Disorder/Other*, OCD, Panic Disorder and PTSD combined

Body System/Adverse Event**	ZOLOFT (N=2198)	Placebo (N=1877)
Autonomic Nervous System Disorders		
Ejaculation Failure[1]	14	1
Mouth Dry	15	9
Sweating Increased	6	2
Centr. & Periph. Nerv. System Disorders		
Somnolence	14	7
Dizziness	12	7
Headache	26	24
Paresthesia	3	2
Tremor	8	2
Disorders of Skin and Appendages		
Rash	3	2
Gastrointestinal Disorders		
Anorexia	6	2
Constipation	7	5
Diarrhea/Loose Stools	21	11
Dyspepsia	8	4
Flatulence	4	3
Nausea	27	13
Vomiting	4	2
General		
Fatigue	11	7
Hot Flushes	2	1
Psychiatric Disorders		
Agitation	6	4
Anxiety	4	3
Insomnia	22	11
Libido Decreased	6	1
Nervousness	6	4
Special Senses		
Vision Abnormal	4	2

[1]Primarily ejaculatory delay. Denominator used was for male patients only (N=913 ZOLOFT; N=773 placebo).
*Major depressive disorder and other premarketing controlled trials.
**Included are events reported by at least 2% of patients taking ZOLOFT except the following events, which had an incidence on placebo greater than or equal to ZOLOFT: abdominal pain and pharyngitis.

ADVERSE REACTIONS

During its premarketing assessment, multiple doses of ZOLOFT were administered to over 4000 adult subjects as of February 26, 1998. The conditions and duration of exposure to ZOLOFT varied greatly, and included (in overlapping categories) clinical pharmacology studies, open and double-blind studies, uncontrolled and controlled studies, inpatient and outpatient studies, fixed-dose and titration studies, and studies for multiple indications, including major depressive disorder, OCD, panic disorder and PTSD. Untoward events associated with this exposure were recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of untoward events into a smaller number of standardized event categories.

In the tabulations that follow, a World Health Organization dictionary of terminology has been used to classify reported adverse events. The frequencies presented, therefore, represent the proportion of the over 4000 adult individuals exposed to multiple doses of ZOLOFT who experienced a treatment-emergent adverse event of the type cited on at least one occasion while receiving ZOLOFT. An event was considered treatment-emergent if it occurred for the first time or worsened while receiving therapy following baseline evaluation. It is important to emphasize that events reported during therapy were not necessarily caused by it. The prescriber should be aware that the figures in the tables and tabulations cannot be used to predict the incidence of side effects in the course of usual medical practice

where patient characteristics and other factors differ from those that prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and nondrug factors to the side effect incidence rate in the population studied.

Incidence in Placebo-Controlled Trials—Table 1 enumerates the most common treatment-emergent adverse events associated with the use of ZOLOFT (incidence of at least 5% for ZOLOFT and at least twice that for placebo within at least one of the indications) for the treatment of adult patients with major depressive disorder/other*, OCD, panic disorder and PTSD in placebo-controlled clinical trials. Most patients received doses of 50 to 200 mg/day. Table 2 enumerates treatment-emergent adverse events that occurred in 2% or more of adult patients treated with ZOLOFT and with incidence greater than placebo who participated in controlled clinical trials comparing ZOLOFT with placebo in the treatment of major depressive disorder/other*, OCD, panic disorder and PTSD. Table 2 provides combined data for the pool of studies that are provided separately by indication in Table 1.

[See table 1 at top of page 2753]

[See table 2 on previous page]

Associated with Discontinuation in Placebo-Controlled Clinical Trials

Table 3 lists the adverse events associated with discontinuation of ZOLOFT® (sertraline hydrochloride) treatment (incidence at least twice that for placebo and at least 1% for ZOLOFT in clinical trials) in major depressive disorder/other*, OCD, panic disorder and PTSD.

[See table 3 at right]

Male and Female Sexual Dysfunction with SSRIs

Although changes in sexual desire, sexual performance and sexual satisfaction often occur as manifestations of a psychiatric disorder, they may also be a consequence of pharmacologic treatment. In particular, some evidence suggests that selective serotonin reuptake inhibitors (SSRIs) can cause such untoward sexual experiences. Reliable estimates of the incidence and severity of untoward experiences involving sexual desire, performance and satisfaction are difficult to obtain, however, in part because patients and physicians may be reluctant to discuss them. Accordingly, estimates of the incidence of untoward sexual experience and performance cited in product labeling, are likely to underestimate their actual incidence.

Table 4 below displays the incidence of sexual side effects reported by at least 2% of patients taking ZOLOFT in placebo-controlled trials.

[See table 4 at right]

There are no adequate and well-controlled studies examining sexual dysfunction with sertraline treatment.

Priapism has been reported with all SSRIs.

While it is difficult to know the precise risk of sexual dysfunction associated with the use of SSRIs, physicians should routinely inquire about such possible side effects.

Other Adverse Events in Pediatric Patients—In approximately N=250 pediatric patients treated with ZOLOFT, the overall profile of adverse events was generally similar to that seen in adult studies, as shown in Tables 1 and 2. However, the following adverse events, not appearing in Tables 1 and 2, were reported at an incidence of at least 2% and occurred at a rate of at least twice the placebo rate in a controlled trial (N=187): hyperkinesia, twitching, fever, malaise, purpura, weight decrease, concentration impaired, manic reaction, emotional lability, thinking abnormal, and epistaxis.

Other Events Observed During the Premarketing Evaluation of ZOLOFT® (sertraline hydrochloride)—Following is a list of treatment-emergent adverse events reported during premarketing assessment of ZOLOFT in clinical trials (over 4000 adult subjects) except those already listed in the previous tables or elsewhere in labeling.

In the tabulations that follow, a World Health Organization dictionary of terminology has been used to classify reported adverse events. The frequencies presented, therefore, represent the proportion of the over 4000 adult individuals exposed to multiple doses of ZOLOFT who experienced an event of the type cited on at least one occasion while receiving ZOLOFT. All events are included except those already listed in the previous tables or elsewhere in labeling and those reported in terms so general as to be uninformative and those for which a causal relationship to ZOLOFT treatment seemed remote. It is important to emphasize that although the events reported occurred during treatment with ZOLOFT, they were not necessarily caused by it.

Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring on one or more occasions in at least 1/100 patients; infrequent adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients. Events of major clinical importance are also described in the PRECAUTIONS section.

Autonomic Nervous System Disorders—*Frequent:* impotence; *Infrequent:* flushing, increased saliva, cold clammy skin, mydriasis; *Rare:* pallor, glaucoma, priapism, vasodilation.

Body as a Whole—General Disorders—*Rare:* allergic reaction, allergy.

Cardiovascular—*Frequent:* palpitations, chest pain; *Infrequent:* hypertension, tachycardia, postural dizziness, postural hypotension, periorbital edema, peripheral edema, hypotension, peripheral ischemia, syncope, edema, dependent edema; *Rare:* precordial chest pain, substernal chest pain, aggravated hypertension, myocardial infarction, cerebrovascular disorder.

Central and Peripheral Nervous System Disorders—*Frequent:* hypertonia, hypoesthesia; *Infrequent:* twitching, confusion, hyperkinesia, vertigo, ataxia, migraine, abnormal coordination, hyperesthesia, leg cramps, abnormal gait, nystagmus, hypokinesia; *Rare:* dysphonia, coma, dyskinesia, hypotonia, ptosis, choreoathetosis, hyporeflexia.

Disorders of Skin and Appendages—*Infrequent:* pruritus, acne, urticaria, alopecia, dry skin, erythematous rash, photosensitivity reaction, maculopapular rash; *Rare:* follicular rash, eczema, dermatitis, contact dermatitis, bullous eruption, hypertrichosis, skin discoloration, pustular rash.

Endocrine Disorders—*Rare:* exophthalmos, gynecomastia.

Gastrointestinal Disorders—*Frequent:* appetite increased; *Infrequent:* dysphagia, tooth caries aggravated, eructation, esophagitis, gastroenteritis; *Rare:* melena, glossitis, gum hyperplasia, hiccup, stomatitis, tenesmus, colitis, diverticulitis, fecal incontinence, gastritis, rectum hemorrhage, hemorrhagic peptic ulcer, proctitis, ulcerative stomatitis, tongue edema, tongue ulceration.

General—*Frequent:* back pain, asthenia, malaise, weight increase; *Infrequent:* fever, rigors, generalized edema; *Rare:* face edema, aphthous stomatitis.

Hearing and Vestibular Disorders—*Rare:* hyperacusis, labyrinthine disorder.

Hematopoietic and Lymphatic—*Rare:* anemia, anterior chamber eye hemorrhage.

Liver and Biliary System Disorders—*Rare:* abnormal hepatic function.

Metabolic and Nutritional Disorders—*Infrequent:* thirst; *Rare:* hypoglycemia, hypoglycemia reaction.

Musculoskeletal System Disorders—*Frequent:* myalgia; *Infrequent:* arthralgia, dystonia, arthrosis, muscle cramps, muscle weakness.

Psychiatric Disorders—*Frequent:* yawning, other male sexual dysfunction, other female sexual dysfunction; *Infrequent:* depression, amnesia, paroniria, teeth-grinding, emotional lability, apathy, abnormal dreams, euphoria, paranoid reaction, hallucination, aggressive reaction, aggravated depression, delusions; *Rare:* withdrawal syndrome, suicide ideation, libido increased, somnambulism, illusion.

Reproductive—*Infrequent:* menstrual disorder, dysmenorrhea, intermenstrual bleeding, vaginal hemorrhage, amenorrhea, leukorrhea; *Rare:* female breast pain, menorrhagia, balanoposthitis, breast enlargement, atrophic vaginitis, acute female mastitis.

Respiratory System Disorders—*Frequent:* rhinitis; *Infrequent:* coughing, dyspnea, upper respiratory tract infection, epistaxis, bronchospasm, sinusitis; *Rare:* hyperventilation, bradypnea, stridor, apnea, bronchitis, hemoptysis, hypoventilation, laryngismus, laryngitis.

Special Senses—*Frequent:* tinnitus; *Infrequent:* conjunctivitis, earache, eye pain, abnormal accommodation; *Rare:* xerophthalmia, photophobia, diplopia, abnormal lacrimation, scotoma, visual field defect.

Urinary System Disorders—*Infrequent:* micturition frequency, polyuria, urinary retention, dysuria, nocturia, urinary incontinence; *Rare:* cystitis, oliguria, pyelonephritis, hematuria, renal pain, strangury.

Laboratory Tests—In man, asymptomatic elevations in serum transaminases (SGOT [or AST] and SGPT [or ALT]) have been reported infrequently (approximately 0.8%) in association with ZOLOFT® (sertraline hydrochloride) administration. These hepatic enzyme elevations usually occurred within the first 1 to 9 weeks of drug treatment and promptly diminished upon drug discontinuation.

ZOLOFT therapy was associated with small mean increases in total cholesterol (approximately 3%) and triglycerides (approximately 5%), and a small mean decrease in serum uric acid (approximately 7%) of no apparent clinical importance.

The safety profile observed with ZOLOFT treatment in patients with major depressive disorder, OCD, panic disorder and PTSD is similar.

Other Events Observed During the Postmarketing Evaluation of ZOLOFT—Reports of adverse events temporally associated with ZOLOFT that have been received since market introduction, that are not listed above and that may have no causal relationship with the drug, include the following: acute renal failure, anaphylactoid reaction, angioedema, blindness, optic neuritis, cataract, increased coagulation times, bradycardia, AV block, atrial arrhythmias, QT-interval prolongation, ventricular tachycardia (including torsade de pointes-type arrhythmias), hypothyroidism, agranulocytosis, aplastic anemia and pancytopenia, leukopenia, thrombocytopenia, lupus-like syndrome, serum sickness, hyperglycemia, galactorrhea, hyperprolactinemia, neuroleptic malignant syndrome-like events, extrapyramidal symptoms, oculogyric crisis, serotonin syndrome, psychosis, pulmonary hypertension, severe skin reactions, which potentially can be fatal, such as Stevens-Johnson syndrome, vasculitis, photosensitivity and other severe cutaneous disorders, rare reports of pancreatitis, and liver events—clinical features (which in the majority of cases appeared to be reversible with discontinuation of ZOLOFT) occurring in one or more patients include: elevated enzymes, increased bilirubin, hepatomegaly, hepatitis, jaundice, abdominal pain, vomiting, liver failure and death.

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class—ZOLOFT® (sertraline hydrochloride) is not a controlled substance.

Physical and Psychological Dependence—In a placebo-controlled, double-blind, randomized study of the comparative abuse liability of ZOLOFT, alprazolam, and d-amphetamine in humans, ZOLOFT did not produce the positive subjective effects indicative of abuse potential, such as euphoria or

Continued on next page

TABLE 3
MOST COMMON ADVERSE EVENTS ASSOCIATED WITH DISCONTINUATION IN PLACEBO-CONTROLLED CLINICAL TRIALS

Adverse Event	Major Depressive Disorder/Other*, OCD, Panic Disorder and PTSD combined (N=2198)	Major Depressive Disorder/Other* (N=861)	OCD (N=533)	Panic Disorder (N=430)	PTSD (N=374)
Agitation	1%	1%	–	2%	–
Diarrhea	2%	2%	2%	1%	–
Dizziness	1%	–	1%	–	–
Dry Mouth	–	1%	–	–	–
Dyspepsia	–	–	–	1%	–
Ejaculation Failure[1]	1%	1%	1%	2%	–
Headache	1%	2%	–	–	1%
Insomnia	2%	1%	3%	2%	–
Nausea	3%	4%	3%	3%	2%
Nervousness	–	–	–	2%	–
Somnolence	2%	1%	2%	2%	–
Tremor	–	2%	–	–	–

[1]Primarily ejaculatory delay. Denominator used was for male patients only (N=271 major depressive disorder/other*; N=296 OCD; N=216 panic disorder; N=130 PTSD).
*Major depressive disorder and other premarketing controlled trials.

TABLE 4

Treatment	Ejaculation failure (primarily delayed ejaculation)		Decreased libido	
	N (males only)	Incidence	N (males and females)	Incidence
ZOLOFT	913	14%	2198	6%
Placebo	773	1%	1877	1%

drug liking, that were observed with the other two drugs. Premarketing clinical experience with ZOLOFT did not reveal any tendency for a withdrawal syndrome or any drug-seeking behavior. In animal studies ZOLOFT does not demonstrate stimulant or barbiturate-like (depressant) abuse potential. As with any CNS active drug, however, physicians should carefully evaluate patients for history of drug abuse and follow such patients closely, observing them for signs of ZOLOFT misuse or abuse (e.g., development of tolerance, incrementation of dose, drug-seeking behavior).

OVERDOSAGE

Human Experience—Of 1,027 cases of overdose involving sertraline hydrochloride worldwide, alone or with other drugs, there were 72 deaths (circa 1999).

Among 634 overdoses in which sertraline hydrochloride was the only drug ingested, 8 resulted in fatal outcome, 75 completely recovered, and 27 patients experienced sequelae after overdosage to include alopecia, decreased libido, diarrhea, ejaculation disorder, fatigue, insomnia, somnolence and serotonin syndrome. The remaining 524 cases had an unknown outcome. The most common signs and symptoms associated with non-fatal sertraline hydrochloride overdosage were somnolence, vomiting, tachycardia, nausea, dizziness, agitation and tremor.

The largest known ingestion was 13.5 grams in a patient who took sertraline hydrochloride alone and subsequently recovered. However, another patient who took 2.5 grams of sertraline hydrochloride alone experienced a fatal outcome. Other important adverse events reported with sertraline hydrochloride overdose (single or multiple drugs) include bradycardia, bundle branch block, coma, convulsions, delirium, hallucinations, hypertension, hypotension, manic reaction, pancreatitis, QT-interval prolongation, serotonin syndrome, stupor and syncope.

Overdose Management—Treatment should consist of those general measures employed in the management of overdosage with any antidepressant.

Ensure an adequate airway, oxygenation and ventilation. Monitor cardiac rhythm and vital signs. General supportive and symptomatic measures are also recommended. Induction of emesis is not recommended. Gastric lavage with a large-bore orogastric tube with appropriate airway protection, if needed, may be indicated if performed soon after ingestion, or in symptomatic patients.

Activated charcoal should be administered. Due to large volume of distribution of this drug, forced diuresis, dialysis, hemoperfusion and exchange transfusion are unlikely to be of benefit. No specific antidotes for sertraline are known.

In managing overdosage, consider the possibility of multiple drug involvement. The physician should consider contacting a poison control center on the treatment of any overdose. Telephone numbers for certified poison control centers are listed in the *Physicians' Desk Reference*® (PDR®).

DOSAGE AND ADMINISTRATION

Initial Treatment

Dosage for Adults

Major Depressive Disorder and Obsessive-Compulsive Disorder—ZOLOFT treatment should be administered at a dose of 50 mg once daily.

Panic Disorder and Posttraumatic Stress Disorder—ZOLOFT treatment should be initiated with a dose of 25 mg once daily. After one week, the dose should be increased to 50 mg once daily.

While a relationship between dose and effect has not been established for major depressive disorder, OCD, panic disorder or PTSD, patients were dosed in a range of 50–200 mg/day in the clinical trials demonstrating the effectiveness of ZOLOFT for the treatment of these indications. Consequently, a dose of 50 mg, administered once daily, is recommended as the initial dose. Patients not responding to a 50 mg dose may benefit from dose increases up to a maximum of 200 mg/day. Given the 24 hour elimination half-life of ZOLOFT, dose changes should not occur at intervals of less than 1 week.

ZOLOFT should be administered once daily, either in the morning or evening.

Dosage for Pediatric Population (Children and Adolescents)

Obsessive-Compulsive Disorder—ZOLOFT treatment should be initiated with a dose of 25 mg once daily in children (ages 6–12) and at a dose of 50 mg once daily in adolescents (ages 13–17).

While a relationship between dose and effect has not been established for OCD, patients were dosed in a range of 25–200 mg/day in the clinical trials demonstrating the effectiveness of ZOLOFT for pediatric patients (6–17 years) with OCD. Patients not responding to an initial dose of 25 or 50 mg/day may benefit from dose increases up to a maximum of 200 mg/day. For children with OCD, their generally lower body weights compared to adults should be taken into consideration in advancing the dose, in order to avoid excess dosing. Given the 24 hour elimination half-life of ZOLOFT, dose changes should not occur at intervals of less than 1 week.

ZOLOFT should be administered once daily, either in the morning or evening.

Dosage for Hepatically Impaired Patients

The use of sertraline in patients with liver disease should be approached with caution. The effects of sertraline in patients with moderate and severe hepatic impairment have not been studied. If sertraline is administered to patients with liver impairment, a lower or less frequent dose should be used (see CLINICAL PHARMACOLOGY and PRECAUTIONS).

Maintenance/Continuation/Extended Treatment

Major Depressive Disorder—It is generally agreed that acute episodes of major depressive disorder require several months or longer of sustained pharmacologic therapy beyond response to the acute episode. Systematic evaluation of ZOLOFT has demonstrated that its antidepressant efficacy is maintained for periods of up to 44 weeks following 8 weeks of initial treatment at a dose of 50–200 mg/day (mean dose of 70 mg/day) (see Clinical Trials under CLINICAL PHARMACOLOGY). It is not known whether the dose of ZOLOFT needed for maintenance treatment is identical to the dose needed to achieve an initial response. Patients should be periodically reassessed to determine the need for maintenance treatment.

Posttraumatic Stress Disorder—It is generally agreed that PTSD requires several months or longer of sustained pharmacological therapy beyond response to initial treatment. Systematic evaluation of ZOLOFT has demonstrated that its efficacy in PTSD is maintained for periods of up to 28 weeks following 24 weeks of treatment at a dose of 50–200 mg/day (see Clinical Trials under CLINICAL PHARMACOLOGY). It is not known whether the dose of ZOLOFT needed for maintenance treatment is identical to the dose needed to achieve an initial response. Patients should be periodically reassessed to determine the need for maintenance treatment.

Obsessive-Compulsive Disorder and Panic Disorder—Although the efficacy of ZOLOFT beyond 10–12 weeks of dosing for OCD and Panic Disorder has not been systematically demonstrated in controlled trials, both are chronic conditions, and it is reasonable to consider continuation of a responding patient. Dosage adjustments may be needed to maintain the patient on the lowest effective dosage and patients should be periodically reassessed to determine the need for continued treatment.

Switching Patients to or from a Monoamine Oxidase Inhibitor—At least 14 days should elapse between discontinuation of an MAOI and initiation of therapy with ZOLOFT. In addition, at least 14 days should be allowed after stopping ZOLOFT before starting an MAOI (see CONTRAINDICATIONS and WARNINGS).

ZOLOFT Oral Concentrate

ZOLOFT Oral Concentrate contains 20 mg/mL of sertraline (as the hydrochloride) as the active ingredient and 12% alcohol. ZOLOFT Oral Concentrate must be diluted before use. Just before taking, use the dropper provided to remove the required amount of ZOLOFT Oral Concentrate and mix with 4 oz (1/2 cup) of water, ginger ale, lemon/lime soda, lemonade or orange juice ONLY. Do not mix ZOLOFT Oral Concentrate with anything other than the liquids listed. The dose should be taken immediately after mixing. Do not mix in advance. At times, a slight haze may appear after mixing; this is normal. Note that caution should be exercised for patients with latex sensitivity, as the dropper dispenser contains dry natural rubber.

ZOLOFT oral concentrate is contraindicated with ANTABUSE (disulfiram) due to the alcohol content of the concentrate.

HOW SUPPLIED

ZOLOFT® (sertraline hydrochloride) capsular-shaped scored tablets, containing sertraline hydrochloride equivalent to 25, 50 and 100 mg of sertraline, are packaged in bottles.

ZOLOFT® 25 mg Tablets: light green film coated tablets engraved on one side with ZOLOFT and on the other side scored and engraved with 25 mg.

NDC 0049-4960-50	Bottles of 50

ZOLOFT® 50 mg Tablets: light blue film coated tablets engraved on one side with ZOLOFT and on the other side scored and engraved with 50 mg.

NDC 0049-4900-66	Bottles of 100
NDC 0049-4900-73	Bottles of 500
NDC 0049-4900-94	Bottles of 5000
NDC 0049-4900-41	Unit Dose Packages of 100

ZOLOFT® 100 mg Tablets: light yellow film coated tablets engraved on one side with ZOLOFT and on the other side scored and engraved with 100 mg.

NDC 0049-4910-66	Bottles of 100
NDC 0049-4910-73	Bottles of 500
NDC 0049-4910-94	Bottles of 5000
NDC 0049-4910-41	Unit Dose Packages of 100

Store at controlled room temperature, 59° to 86°F (15° to 30°C).

ZOLOFT® Oral Concentrate: ZOLOFT Oral Concentrate is a clear, colorless solution with a menthol scent containing sertraline hydrochloride equivalent to 20 mg of sertraline per mL and 12% alcohol. It is supplied as a 60 mL bottle with an accompanying calibrated dropper.

NDC 0049-4940-23	Bottles of 60 mL

Store at controlled room temperature, 59° to 86°F (15° to 30°C).

Rx only

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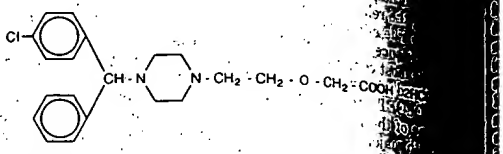
Shown in Product Identification Guide, page 332

ZYRTEC® ℞
(cetirizine hydrochloride)
Tablets and Syrup
For Oral Use

DESCRIPTION

Cetirizine hydrochloride, the active component of ZYRTEC® tablets and syrup, is an orally active and selective H_1-receptor antagonist. The chemical name is [4- [(4-chlorophenyl)phenylmethyl] -1- piperazinyl]-acetic acid, dihydrochloride. Cetirizine hydrochloride is a racemic compound with an empirical formula of $C_{21}H_{25}ClN_2O_3 \cdot 2HCl$. The molecular weight is 461.82. The chemical structure is shown below:



Cetirizine hydrochloride is a white, crystalline powder that is water soluble. ZYRTEC tablets are formulated as white, film-coated, rounded-off rectangular shaped tablets for oral administration and are available in 5 and 10 mg strengths. Inactive ingredients are: lactose; magnesium stearate; povidone; titanium dioxide; hydroxypropyl methylcellulose; polyethylene glycol; and corn starch.

ZYRTEC syrup is a colorless to slightly yellow syrup containing cetirizine hydrochloride at a concentration of 1 mg/mL (5 mg/5 mL) for oral administration. The pH is between 4 and 5. The inactive ingredients of the syrup are: banana flavor; glacial acetic acid; glycerin; grape flavor; methylparaben; propylene glycol; propylparaben; sodium acetate; sugar syrup; and water.

CLINICAL PHARMACOLOGY

Mechanism of Actions: Cetirizine, a human metabolite of hydroxyzine, is an antihistamine; its principal effects are mediated via selective inhibition of peripheral H_1 receptors. The antihistaminic activity of cetirizine has been clearly documented in a variety of animal and human models *in vivo* and *ex vivo* animal models have shown negligible anticholinergic and antiserotonergic activity. In clinical studies, however, dry mouth was more common with cetirizine than with placebo. *In vitro* receptor binding studies have shown no measurable affinity for other than H_1 receptors. Autoradiographic studies with radiolabeled cetirizine in the rat have shown negligible penetration into the brain. Ex-vivo experiments in the mouse have shown that systemically administered cetirizine does not significantly occupy cerebral H_1 receptors.

Pharmacokinetics:

Absorption: Cetirizine was rapidly absorbed with a T_{max} to maximum concentration (T_{max}) of approximately 1 hr following oral administration of tablets or syrup in adults. Comparable bioavailability was found between the tablet and syrup dosage forms. When healthy volunteers were administered multiple doses of cetirizine (10 mg tablets once daily for 10 days), a mean peak plasma concentration (C_{max}) of 311 ng/mL was observed. No accumulation was observed. Cetirizine pharmacokinetics were linear for oral doses ranging from 5 to 60 mg. Food had no effect on the extent of cetirizine exposure (AUC) but T_{max} was delayed by 1 hours and C_{max} was decreased by 23% in the presence of food.

Distribution: The mean plasma protein binding of cetirizine is 93%, independent of concentration in the range of 25–1000 ng/mL, which includes the therapeutic plasma levels observed.

Metabolism: A mass balance study in 6 healthy male volunteers indicated that 70% of the administered radioactivity was recovered in the urine and 10% in the feces. Approximately 50% of the radioactivity was identified in the urine as unchanged drug. Most of the rapid increase in peak plasma radioactivity was associated with parent drug, suggesting a low degree of first-pass metabolism. Cetirizine is metabolized to a limited extent by oxidative O-dealkylation to a metabolite with negligible antihistaminic activity. The enzyme or enzymes responsible for this metabolism have not been identified.

Elimination: The mean elimination half-life in 146 healthy volunteers across multiple pharmacokinetic studies was 8.3 hours and the apparent total body clearance for cetirizine was approximately 53 mL/min.

Interaction Studies

Pharmacokinetic interaction studies with cetirizine in adults were conducted with pseudoephedrine, antipyrine, ketoconazole, erythromycin and azithromycin. No interactions were observed. In a multiple dose study of theophylline (400 mg once daily for 3 days) and cetirizine (20 mg once daily for 3 days), a 16% decrease in the clearance of cetirizine was observed. The disposition of theophylline was not altered by concomitant cetirizine administration.

Special Populations

Pediatric Patients: When pediatric patients aged 7 to 9 years received a single, 5-mg oral cetirizine capsule, the mean C_{max} was 275 ng/mL. Based on cross-study comparisons, the weight-normalized, apparent total body clearance was 33% greater and the elimination half-life was 30% shorter in this pediatric population than in adults. In pediatric patients aged 2 to 5 years who received 5 mg of cetirizine, the mean C_{max} was 660 ng/mL. Based on cross-study comparisons, the weight-normalized apparent total body clearance was 81 to 111% greater and the elimination half-life was 33 to 41% shorter in this pediatric population than in adults.

Geriatric Patients: Following a single, 10-mg oral dose, the elimination half-life was prolonged by 50% and the apparent total body clearance was 40% lower in 16 geriatric subjects with a mean age of 77 years compared to 14 adult subjects with a mean age of 53 years. The decrease in cetirizine clearance in these elderly volunteers may be related to decreased renal function.

continuation of the drug alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation and treatment with an antibacterial drug effective against *Clostridium difficile*.

PRECAUTIONS

General

DURICEF should be used with caution in the presence of markedly impaired renal function (creatinine clearance rate of less than 50 mL/min/1.73 M^2). (See DOSAGE AND ADMINISTRATION.) In patients with known or suspected renal impairment, careful clinical observation and appropriate laboratory studies should be made prior to and during therapy.

Prolonged use of DURICEF may result in the overgrowth of nonsusceptible organisms. Careful observation of the patient is essential. If superinfection occurs during therapy, appropriate measures should be taken.

DURICEF® (cefadroxil monohydrate, USP) should be prescribed with caution in individuals with history of gastrointestinal disease, particularly colitis.

Drug/Laboratory Test Interactions

Positive direct Coombs' tests have been reported during treatment with the cephalosporin antibiotics. In hematologic studies or in transfusion cross-matching procedures when antiglobulin tests are performed on the minor side or in Coombs' testing of newborns whose mothers have received cephalosporin antibiotics before parturition, it should be recognized that a positive Coombs' test may be due to the drug.

Carcinogenesis, Mutagenesis, and Impairment of Fertility: No long-term studies have been performed to determine carcinogenic potential. No genetic toxicity tests have been performed.

Pregnancy: Pregnancy Category B. Reproduction studies have been performed in mice and rats at doses up to 11 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to cefadroxil monohydrate. There are, however, no adequate and well controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Labor and Delivery: DURICEF (cefadroxil monohydrate, USP) has not been studied for use during labor and delivery. Treatment should only be given if clearly needed.

Nursing Mothers: Caution should be exercised when cefadroxil monohydrate is administered to a nursing mother.

Pediatric Use: (See DOSAGE AND ADMINISTRATION.)

ADVERSE REACTIONS

Gastrointestinal

Onset of pseudomembranous colitis symptoms may occur during or after antibiotic treatment (see WARNINGS). Dyspepsia, nausea and vomiting have been reported rarely. Diarrhea has also occurred.

Hypersensitivity

Allergies (in the form of rash, urticaria, angioedema, and pruritis) have been observed. These reactions usually subsided upon discontinuation of the drug. Anaphylaxis has also been reported.

Other

Other reactions have included hepatic dysfunction including cholestasis and elevations in serum transaminase, genital pruritus, genital moniliasis, vaginitis, moderate transient neutropenia, fever. Agranulocytosis, thrombocytopenia, idiosyncratic hepatic failure, erythema multiforme, Stevens-Johnson syndrome, serum sickness, and arthralgia have been rarely reported.

In addition to the adverse reactions listed above which have been observed in patients treated with cefadroxil, the following adverse reactions and altered laboratory tests have been reported for cephalosporin-class antibiotics: Toxic epidermal necrolysis, abdominal pain, superinfection, renal dysfunction, toxic nephropathy, aplastic anemia, hemolytic anemia, hemorrhage, prolonged prothrombin time, positive Coombs' test, increased BUN, increased creatinine, elevated alkaline phosphatase, elevated aspartate aminotransferase (AST), elevated alanine aminotransferase (ALT), elevated bilirubin, elevated LDH, eosinophilia, pancytopenia, neutropenia.

Several cephalosporins have been implicated in triggering seizures, particularly in patients with renal impairment, when the dosage was not reduced (see DOSAGE AND ADMINISTRATION and OVERDOSAGE). If seizures associated with drug therapy occur, the drug should be discontinued. Anticonvulsant therapy can be given if clinically indicated.

OVERDOSAGE

A study of children under six years of age suggested that ingestion of less than 250 mg/kg of cephalosporins is not associated with significant outcomes. No action is required other than general support and observation. For amounts greater than 250 mg/kg, induce gastric emptying.

In five anuric patients, it was demonstrated that an average of 63% of a 1 g oral dose is extracted from the body during a 6-8 hour hemodialysis session.

DOSAGE AND ADMINISTRATION

DURICEF is acid-stable and may be administered orally without regard to meals. Administration with food may be helpful in diminishing potential gastrointestinal complaints occasionally associated with oral cephalosporin therapy.

Adults

Urinary Tract Infections: For uncomplicated lower urinary tract infections (i.e., cystitis) the usual dosage is 1 or 2 g per day in single (q.d.) or divided doses (b.i.d.).

For all other urinary tract infections the usual dosage is 2 g per day in divided doses (b.i.d.).

Skin and Skin Structure Infections: For skin and skin structure infections the usual dosage is 1 g per day in single (q.d.) or divided doses (b.i.d.).

Pharyngitis and Tonsillitis: Treatment of group A beta-hemolytic streptococcal pharyngitis and tonsillitis—1 g per day in single (q.d.) or divided doses (b.i.d.) for 10 days.

Children

For urinary tract infections, the recommended daily dosage for children is 30 mg/kg/day in divided doses every 12 hours.

For pharyngitis, tonsillitis, and impetigo, the recommended daily dosage for children is 30 mg/kg/day in a single dose or in equally divided doses every 12 hours. For other skin and skin structure infections, the recommended daily dosage is 30 mg/kg/day in equally divided doses every 12 hours. In the treatment of beta-hemolytic streptococcal infections, a therapeutic dosage of DURICEF should be administered for at least 10 days.

See chart for total daily dosage for children.

[See first table at top right of previous page]

In patients with renal impairment, the dosage of cefadroxil monohydrate should be adjusted according to creatinine clearance rates to prevent drug accumulation. The following schedule is suggested. In adults, the initial dose is 1000 mg of DURICEF (cefadroxil monohydrate, USP) and the maintenance dose (based on the creatinine clearance rate [mL/min/1.73 M^2]) is 500 mg at the time intervals listed below.

[See second table at top right of previous page]

Patients with creatinine clearance rates over 50 mL/min may be treated as if they were patients having normal renal function.

[See table below]

HOW SUPPLIED

DURICEF® (cefadroxil monohydrate, USP) 500 mg Capsules: opaque, maroon and white hard gelatin capsules, imprinted with "PPP" and "784" on one end and with "DURICEF" and "500 mg" on the other end. Capsules are supplied as follows:

NDC 0087-0784-46 Bottle of 50

Store at controlled room temperature (15°-30°C).

DURICEF® 1 gram Tablets: white to off white, top bisected, oval shaped, imprinted with "PPP" on one side of the bisect and "785" on the other side of the bisect. Tablets are supplied as follows:

NDC 0087-0785-43 Bottle of 50

NDC 0087-0785-45 4 packs of 10 individually labeled blisters with 1 tablet per blister

Store at controlled room temperature (15°-30°C).

DURICEF® for Oral Suspension is orange-pineapple flavored, and is supplied as follows:

125 mg/5 mL	**NDC** 0087-0786-41	100 mL Bottle
250 mg/5 mL	**NDC** 0087-0782-41	100 mL Bottle
500 mg/5 mL	**NDC** 0087-0783-05	75 mL Bottle
	NDC 0087-0783-41	100 mL Bottle

Prior to reconstitution: Store at controlled room temperature (15°-30°C).

Reconstitution Directions for Oral Suspension

Bottle Size	Reconstitution Directions
100 mL	Suspend in a total of 67 mL water. Method: Tap bottle lightly to loosen powder. Add 67 mL of water in two portions. Shake well after each addition.
75 mL	Suspend in a total of 51 mL water. Method: Tap bottle lightly to loosen powder. Add 51 mL of water in two portions. Shake well after each addition.
50 mL	Suspend in a total of 34 mL water. Method: Tap bottle lightly to loosen powder. Add 34 mL of water in two portions. Shake well after each addition.

After reconstitution, store in refrigerator. Shake well before using. Keep container tightly closed. Discard unused portion after 14 days.

REFERENCES

1. National Committee for Clinical Laboratory Standards, Approved Standard, *Performance Standards for Antimicrobial Disk Susceptibility Test*, 4th Edition, Vol. 10 (7): M2-A4, Villanova, PA, April, 1990. 2. National Committee for Clinical Laboratory Standards, Approved Standard: *Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically*, 2nd Edition, Vol. 10 (8): M7-A2, Villanova, PA, April, 1990.

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Bristol-Myers Squibb Company
Princeton, NJ 08543
USA

Shown in Product Identification Guide, page 309

GLUCOPHAGE®

[GLUE-coe-fahj]

(metformin hydrochloride tablets)

GLUCOPHAGE® XR

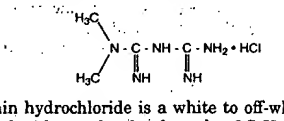
(metformin hydrochloride extended-release tablets)

Rx only

DESCRIPTION

GLUCOPHAGE® (metformin hydrochloride tablets) and GLUCOPHAGE® XR (metformin hydrochloride extended-release tablets) are oral antihyperglycemic drugs used in the management of type 2 diabetes. Metformin hydrochloride (*N,N*-dimethylimidodicarbonimidic diamide hydrochloride) is not chemically or pharmacologically related to any other classes of oral antihyperglycemic agents.

The structural formula is as shown:



Metformin hydrochloride is a white to off-white crystalline compound with a molecular formula of $C_4H_{11}N_5 \cdot HCl$ and a molecular weight of 165.63. Metformin hydrochloride is freely soluble in water and is practically insoluble in acetone, ether, and chloroform. The pKa of metformin is 12.4. The pH of a 1% aqueous solution of metformin hydrochloride is 6.68.

GLUCOPHAGE tablets contain 500 mg, 850 mg, or 1000 mg of metformin hydrochloride. Each tablet contains the inactive ingredients povidone and magnesium stearate. In addition, the coating for the 500-mg and 850-mg tablets contains hydroxypropyl methylcellulose (hypromellose) and the coating for the 1000-mg contains hydroxypropyl methylcellulose and polyethylene glycol.

GLUCOPHAGE XR contains 500 mg of metformin hydrochloride as the active ingredient. Each tablet contains the inactive ingredients sodium carboxymethyl cellulose, hydroxypropyl methylcellulose, microcrystalline cellulose, and magnesium stearate.

System Components and Performance

GLUCOPHAGE XR tablets comprise a dual hydrophilic polymer matrix system. Metformin hydrochloride is combined with a drug release controlling polymer to form an "inner" phase, which is then incorporated as discrete particles into an "external" phase of a second polymer. After administration, fluid from the gastrointestinal (GI) tract enters the tablet, causing the polymers to hydrate and swell. Drug is released slowly from the dosage form by a process of diffusion through the gel matrix that is essentially independent of pH. The hydrated polymer system is not rigid and is expected to be broken up by normal peristalsis in the GI tract. The biologically inert components of the tablet may occasionally remain intact during GI transit and will be eliminated in the feces as a soft, hydrated mass.

CLINICAL PHARMACOLOGY

Mechanism of Action

Metformin is an antihyperglycemic agent which improves glucose tolerance in patients with type 2 diabetes, lowering both basal and postprandial plasma glucose. Its pharmacologic mechanisms of action are different from other classes of oral antihyperglycemic agents. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. Unlike sulfonylureas, metformin does not produce hypoglycemia in either patients with type 2 diabetes or normal subjects (except in special circumstances, see **PRECAUTIONS**) and does not cause hyperinsulinemia. With metformin therapy, insulin secretion remains unchanged while fasting insulin levels and day-long plasma insulin response may actually decrease.

Pharmacokinetics

Absorption and Bioavailability

The absolute bioavailability of a GLUCOPHAGE 500-mg tablet given under fasting conditions is approximately 50-60%. Studies using single oral doses of GLUCOPHAGE 500 mg to 1500 mg, and 850 mg to 2550 mg, indicate that there is a lack of dose proportionality with increasing dose, which is due to decreased absorption rather than an alteration in elimination. Food decreases the extent of and slightly delays the absorption of metformin, as shown by approximately a 40% lower mean peak plasma concentration (C_{max}), a 25% lower area under the plasma concentration versus time curve (AUC), and a 35 minute prolongation in time to peak plasma concentration (T_{max}) following administration of a single 850-mg tablet of metformin with food compared to the same tablet strength administered fasting. The clinical relevance of these decreases is unknown.

Following a single oral dose of GLUCOPHAGE XR, C_{max} is achieved with a median value of 7 hours and a range

hours. Peak plasma levels are approximately compared to the same dose of GLUCOPHAGE, the extent of absorption (as measured by AUC) is GLUCOPHAGE. the AUC and C_{max} are less than dose pro- GLUCOPHAGE XR within the range of 500 administered once daily. Peak plasma levels mg, once-daily doses, respectively. The ex- metformin absorption (as measured by AUC) from GLUCOPHAGE XR at a 2000 mg once-daily dose is similar the same total daily dose administered as tablets 1000 mg twice daily. After repeated GLUCOPHAGE XR, metformin did not accumulate in plasma.

Within-subject variability in C_{max} and AUC of metformin from GLUCOPHAGE XR is comparable to that with GLUCOPHAGE.

Although the extent of metformin absorption (as measured by AUC) from the GLUCOPHAGE XR tablet increased by approximately 50% when given with food, there was no effect of food on C_{max} and T_{max} of metformin. Both high and low fat meals had the same effect on the pharmacokinetics of GLUCOPHAGE XR.

Distribution

The apparent volume of distribution (V/F) of metformin following single oral doses of GLUCOPHAGE 850 mg averaged 654±358 L. Metformin is negligibly bound to plasma proteins in contrast to sulfonylureas, which are more than 90% protein bound. Metformin partitions into erythrocytes, most likely as a function of time. At usual clinical doses and dosing schedules of GLUCOPHAGE, steady-state plasma concentrations of metformin are reached within 24-48 hours and are generally <1 µg/mL. During controlled clinical trials of GLUCOPHAGE, maximum metformin plasma levels did not exceed 5 µg/mL, even at maximum doses.

Metabolism and Elimination

Intravenous single-dose studies in normal subjects demonstrate that metformin is excreted unchanged in the urine and does not undergo hepatic metabolism (no metabolites have been identified in humans) nor biliary excretion. Renal clearance (see **Table 1**) is approximately 3.5 times greater than creatinine clearance, which indicates that tubular secretion is the major route of metformin elimination. Following oral administration, approximately 90% of the absorbed drug is eliminated via the renal route within the first 24 hours, with a plasma elimination half-life of approximately 6.2 hours. In blood, the elimination half-life is approximately 17.6 hours, suggesting that the erythrocyte mass may be a compartment of distribution.

Special Populations

Patients with Type 2 Diabetes

In the presence of normal renal function, there are no differences between single- or multiple-dose pharmacokinetics of metformin between patients with type 2 diabetes and normal subjects (see **Table 1**), nor is there any accumulation of metformin in either group at usual clinical doses. The pharmacokinetics of GLUCOPHAGE XR in patients with type 2 diabetes are comparable to those in healthy normal adults.

Renal Insufficiency

In patients with decreased renal function (based on measured creatinine clearance), the plasma and blood half-life of metformin is prolonged and the renal clearance is decreased in proportion to the decrease in creatinine clearance (see **Table 1**; also see **WARNINGS**).

Hepatic Insufficiency

No pharmacokinetic studies of metformin have been conducted in patients with hepatic insufficiency.

Geriatrics

Limited data from controlled pharmacokinetic studies of GLUCOPHAGE in healthy elderly subjects suggest that total plasma clearance of metformin is decreased, the half-life is prolonged, and C_{max} is increased, compared to healthy young subjects. From these data, it appears that the change in metformin pharmacokinetics with aging is primarily accounted for by a change in renal function (see **Table 1**). GLUCOPHAGE and GLUCOPHAGE XR (metformin hydrochloride extended-release tablets) treatment should not be initiated in patients ≥ 80 years of age unless measurement of creatinine clearance demonstrates that renal function is not reduced. (See **WARNINGS** and **DOSAGE AND ADMINISTRATION**.)

See table 1 above.

Pediatrics

No pharmacokinetic data from studies of pediatric patients are currently available.

Gender

Metformin pharmacokinetic parameters did not differ significantly between normal subjects and patients with type 2 diabetes when analyzed according to gender (males = 19, females = 16). Similarly, in controlled clinical studies in patients with type 2 diabetes, the antihyperglycemic effect of GLUCOPHAGE (metformin hydrochloride tablets) was comparable in males and females.

Race

No studies of metformin pharmacokinetic parameters according to race have been performed. In controlled clinical studies of GLUCOPHAGE in patients with type 2 diabetes, the antihyperglycemic effect was comparable in whites (n=249), blacks (n=51), and Hispanics (n=24).

Table 1. Select Mean (±S.D.) Metformin Pharmacokinetic Parameters Following Single or Multiple Oral Doses of GLUCOPHAGE

Subject Groups: GLUCOPHAGE dose[a] (number of subjects)	C_{max}[b] (µg/mL)	T_{max}[c] (hrs)	Renal Clearance (mL/min)
Healthy, nondiabetic adults:			
500 mg single dose (24)	1.03 (±0.33)	2.75 (±0.81)	600 (±132)
850 mg single dose (74)[d]	1.60 (±0.38)	2.64 (±0.82)	552 (±139)
850 mg three times daily for 19 doses[e] (9)	2.01 (±0.42)	1.79 (±0.94)	642 (±173)
Adults with type 2 diabetes:			
850 mg single dose (23)	1.48 (±0.5)	3.32 (±1.08)	491 (±138)
850 mg three times daily for 19 doses[e] (9)	1.90 (±0.62)	2.01 (±1.22)	550 (±160)
Elderly[f], healthy nondiabetic adults:			
850 mg single dose (12)	2.45 (±0.70)	2.71 (±1.05)	412 (±98)
Renal-impaired adults:			
850 mg single dose			
Mild (CL_{cr}[g] 61-90 mL/min) (5)	1.86 (±0.52)	3.20 (±0.45)	384 (±122)
Moderate (CL_{cr} 31-60 mL/min) (4)	4.12 (±1.83)	3.75 (±0.50)	108 (±57)
Severe (CL_{cr} 10-30 mL/min) (6)	3.93 (±0.92)	4.01 (±1.10)	130 (±90)

[a] All doses given fasting except the first 18 doses of the multiple dose studies
[b] Peak plasma concentration
[c] Time to peak plasma concentration
[d] Combined results (average means) of five studies; mean age 32 years (range 23-59 years)
[e] Kinetic study done following dose 19, given fasting
[f] Elderly subjects, mean age 71 years (range 65-81 years)
[g] CL_{cr} = creatinine clearance normalized to body surface area of 1.73 m^2

Table 3. Combined GLUCOPHAGE/Glyburide (Comb) vs Glyburide (Glyb) or GLUCOPHAGE (GLU) Monotherapy: Summary of Mean Changes from Baseline* in Fasting Plasma Glucose HbA_{1c} and Body Weight, at Final Visit (29-week study)

	Comb (n = 213)	Glyb (n = 209)	GLU (n = 210)	p-values Glyb vs Comb	GLU vs Comb	GLU vs Glyb
Fasting Plasma Glucose (mg/dL)						
Baseline	250.5	247.5	253.9	NS**	NS**	NS**
Change at FINAL VISIT	-63.5	13.7	0.9	0.001	0.001	0.025
Hemoglobin A_{1c} (%)						
Baseline	8.8	8.5	8.9	NS**	NS**	0.007
Change at FINAL VISIT	-1.7	0.2	-0.4	0.001	0.001	0.001
Body Weight (lbs)						
Baseline	202.2	203.0	204.0	NS**	NS**	NS**
Change at FINAL VISIT	0.9	-0.7	-8.4	0.011	0.001	0.001

*All patients on glyburide, 20 mg/day, at Baseline
**Not statistically significant

CLINICAL STUDIES

GLUCOPHAGE

In a double-blind, placebo-controlled, multicenter U.S. clinical trial involving obese patients with type 2 diabetes whose hyperglycemia was not adequately controlled with dietary management alone (baseline fasting plasma glucose [FPG] of approximately 240 mg/dL), treatment with GLUCOPHAGE (up to 2550 mg/day) for 29 weeks resulted in significant mean net reductions in fasting and postprandial plasma glucose (PPG) and hemoglobin A_{1c} (HbA_{1c}) of 59 mg/dL, 83 mg/dL, and 1.8%, respectively, compared to the placebo group (see **Table 2**).

Table 2. GLUCOPHAGE vs Placebo Summary of Mean Changes from Baseline* in Fasting Plasma Glucose, HbA_{1c} and Body Weight, at Final Visit (29-week study)

	GLUCOPHAGE (n = 141)	Placebo (n = 145)	p-Value
FPG (mg/dL)			
Baseline	241.5	237.7	NS**
Change at FINAL VISIT	-53.0	6.3	0.001
Hemoglobin A_{1c} (%)			
Baseline	8.4	8.2	NS**
Change at FINAL VISIT	-1.4	0.4	0.001
Body Weight (lbs)			
Baseline	201.0	206.0	NS**
Change at FINAL VISIT	-1.4	-2.4	NS**

*All patients on diet therapy at Baseline
**Not statistically significant

A 29-week, double-blind, placebo-controlled study of GLUCOPHAGE and glyburide, alone and in combination, was conducted in obese patients with type 2 diabetes who had failed to achieve adequate glycemic control while on maximum doses of glyburide (baseline FPG of approximately 250 mg/dL) (see **Table 3**). Patients randomized to the combination arm started therapy with GLUCOPHAGE 500 mg and glyburide 20 mg. At the end of each week of the first four weeks of the trial, these patients had their dosages of GLUCOPHAGE increased by 500 mg if they had failed to reach target fasting plasma glucose. After week four, such dosage adjustments were made monthly, although no tient was allowed to exceed GLUCOPHAGE 2500 mg. tients in the GLUCOPHAGE only arm (metformin plus cebo) followed the same titration schedule. At the end of trial, approximately 70% of the patients in the combina group were taking GLUCOPHAGE 2000 mg/glyburide mg or GLUCOPHAGE 2500 mg/glyburide 20 mg. Patie randomized to continue on glyburide experienced worsen of glycemic control, with mean increases in FPG, PPG, HbA_{1c} of 14 mg/dL, 3 mg/dL and 0.2%, respectively. In trast, those randomized to GLUCOPHAGE (up to 2500 day) experienced a slight improvement, with mean rec tions in FPG, PPG, and HbA_{1c} of 1 mg/dL, 6 mg/dL 0.4%, respectively. The combination GLUCOPHAGE and glyburide was effective in reduc FPG, PPG, and HbA_{1c} levels by 63 mg/dL, 65 mg/dL, 1.7%, respectively. Compared to results of glyburide tr ment alone, the net differences with combination treatm were -77 mg/dL, -68 mg/dL and -1.9%, respectively, (Table 3).

[See table 3 above]

The magnitude of the decline in fasting blood glucose centration following the institution of GLUCOPHA (metformin hydrochloride tablets) therapy was proportio to the level of fasting hyperglycemia. Patients with typ diabetes with higher fasting glucose concentrations exp enced greater declines in plasma glucose and glycosyla hemoglobin.

In clinical studies, GLUCOPHAGE, alone or in combinat with a sulfonylurea, lowered mean fasting serum trigly ides, total cholesterol, and LDL cholesterol levels and l no adverse effects on other lipid levels (see Table 4).

[See table 4 at top of next page]

In contrast to sulfonylureas, body weight of individuals GLUCOPHAGE, tended to remain stable or even decre somewhat (see Tables 2 and 3).

A 24-week, double-blind, placebo-controlled study GLUCOPHAGE plus insulin versus insulin plus plac was conducted in patients with type 2 diabetes who failed achieve adequate glycemic control on insulin alone (see ble 5). Patients randomized to receive GLUCOPHAGE p insulin achieved a reduction in HbA_{1c} of 2.10%, compare a 1.56% reduction in HbA_{1c} achieved by insulin plus cebo. The improvement in glycemic control was achieved the final study visit with 16% less insulin, 93.0 U/day

Continued on next pag

110.6 U/day, GLUCOPHAGE plus insulin versus insulin plus placebo, respectively, p=0.04.

[See table 5 at right]

A second double-blind, placebo-controlled study (n=51), with 16 weeks of randomized treatment, demonstrated that in patients with type 2 diabetes controlled on insulin for 8 weeks with an average HbA_{1c} of 7.46 ± 0.97%, the addition of GLUCOPHAGE maintained similar glycemic control (HbA_{1c} 7.15 ± 0.61 versus 6.97 ± 0.62 for GLUCOPHAGE plus insulin and placebo plus insulin, respectively) with 19% less insulin versus baseline (reduction of 23.68 ± 30.22 versus an increase of 0.43 ± 25.20 units for GLUCOPHAGE plus insulin and placebo plus insulin, p<0.01). In addition, this study demonstrated that the combination of GLUCOPHAGE (metformin hydrochloride tablets) plus insulin resulted in reduction in body weight of 3.11 ± 4.30 lbs, compared to an increase of 1.30 ± 6.08 lbs for placebo plus insulin, p=0.01.

GLUCOPHAGE XR

A 24-week, double-blind, placebo-controlled study of GLUCOPHAGE XR, taken once daily with the evening meal, was conducted in patients with type 2 diabetes who had failed to achieve glycemic control with diet and exercise (HbA_{1c} 7.0-10.0%, FPG 126-270 mg/dL). Patients entering the study had a mean baseline HbA_{1c} of 8.0% and a mean baseline FPG of 176 mg/dL. After 12 weeks treatment, mean HbA_{1c} had increased from baseline by 0.1% and mean FPG decreased from baseline by 2 mg/dL in the placebo group, compared with a decrease in mean HbA_{1c} of 0.6% and a decrease in mean FPG of 23 mg/dL in patients treated with GLUCOPHAGE XR 1000 mg once daily. Subsequently, the treatment dose was increased to 1500 mg once daily if HbA_{1c} was ≥7.0% but <8.0% (patients with HbA_{1c} ≥8.0% were discontinued from the study). At the final visit (24-week), mean HbA_{1c} had increased 0.2% from baseline in placebo patients and decreased 0.6% with GLUCOPHAGE XR (metformin hydrochloride extended-release tablets).

A 16-week, double-blind, placebo-controlled, dose-response study of GLUCOPHAGE XR, taken once daily with the evening meal, or twice daily with meals, was conducted in patients with type 2 diabetes who had failed to achieve glycemic control with diet and exercise (HbA_{1c} 7.0-11%, FPG 126-280 mg/dL). Changes in glycemic control and body weight are shown in **Table 6**.

[See table 6 at right]

Compared with placebo, improvement in glycemic control was seen at all dose levels of GLUCOPHAGE XR and treatment was not associated with any significant change in weight (see **DOSAGE AND ADMINISTRATION** for dosing recommendations for GLUCOPHAGE and GLUCOPHAGE XR).

A 24-week, double-blind, randomized study of GLUCOPHAGE XR, taken once daily with the evening meal, and GLUCOPHAGE, taken twice daily (with breakfast and evening meal), was conducted in patients with type 2 diabetes who had been treated with GLUCOPHAGE 500 mg twice daily for at least 8 weeks prior to study entry. The GLUCOPHAGE dose had not necessarily been titrated to achieve a specific level of glycemic control prior to study entry. Patients qualified for the study if HbA_{1c} was ≤8.5% and FPG was ≤200 mg/dL. Changes in glycemic control and body weight are shown in **Table 7**.

[See table 7 on next page]

After 12 weeks of treatment, there was an increase in mean HbA_{1c} in all groups; in the GLUCOPHAGE XR 1000 mg group, the increase from baseline of 0.23% was statistically significant (see **DOSAGE AND ADMINISTRATION**).

Changes in lipid parameters in the previously described placebo-controlled dose-response study of GLUCOPHAGE XR are shown in **Table 8**.

[See table 8 at bottom of next page]

Changes in lipid parameters in the previously described study of GLUCOPHAGE and GLUCOPHAGE XR are shown in **Table 9**.

Table 9. Summary of Mean Percent Changes from Baseline* in Major Lipid Variables at Final Visit (24-week study)

	GLUCOPHAGE	GLUCOPHAGE XR	
	500 mg Twice Daily	1000 mg Once Daily	1500 mg Once Daily
Total Cholesterol (mg/dL)	(n=68)	(n=70)	(n=66)
Baseline	199.0	201.9	201.6
Mean % change at FINAL VISIT	0.1%	1.3%	0.1%
Total Triglycerides (mg/dL)	(n=68)	(n=70)	(n=66)
Baseline	178.0	169.2	206.8
Mean % change at FINAL VISIT	6.3%	25.3%	33.4%
LDL-Cholesterol (mg/dL)	(n=68)	(n=70)	(n=66)
Baseline	122.1	126.2	115.7
Mean % change at FINAL VISIT	-1.3%	-3.3%	-3.7%
HDL-Cholesterol (mg/dL)	(n=68)	(n=70)	(n=65)
Baseline	41.9	41.7	44.6
Mean % change at FINAL VISIT	4.8%	1.0%	-2.1%

* All patients on GLUCOPHAGE 500 mg twice daily at Baseline

Table 4. Summary of Mean Percent Change from Baseline of Major Serum Lipid Variables at Final Visit (29-week studies)

	GLUCOPHAGE vs Placebo		Combined GLUCOPHAGE/Glyburide vs Monothera		
	GLUCOPHAGE (n = 141)	Placebo (n = 145)	GLUCOPHAGE (n = 210)	GLUCOPHAGE/Glyburide (n = 213)	Glyburide (n = 209)
Total Cholesterol (mg/dL)					
Baseline	211.0	212.3	213.1	215.6	219.6
Mean % change at FINAL VISIT	-5%	1%	-2%	-4%	1%
Total Triglycerides (mg/dL)					
Baseline	236.1	203.5	242.5	215.0	266.1
Mean % change at FINAL VISIT	-16%	1%	-3%	-8%	4%
LDL-Cholesterol (mg/dL)					
Baseline	135.4	138.5	134.3	136.0	137.5
Mean % change at FINAL VISIT	-8%	1%	-4%	-6%	3%
HDL-Cholesterol (mg/dL)					
Baseline	39.0	40.5	37.2	39.0	37.0
Mean % change at FINAL VISIT	2%	-1%	5%	3%	1%

Table 5. Combined GLUCOPHAGE/Insulin vs Placebo/Insulin Summary of Mean Changes from Baseline in HbA_{1c} and Daily Insulin Dose

	GLUCOPHAGE/Insulin n=26	Placebo/Insulin n=28	Treatment difference Mean ± SE
Hemoglobin A_{1c} (%)			
Baseline	8.95	9.32	
Change at FINAL VISIT	-2.10	-1.56	-0.54 ± 0.43[a]
Insulin Dose (U/day)			
Baseline	93.12	94.64	
Change at FINAL VISIT	-0.15	15.93	-16.08 ± 7.77[b]

[a] Statistically significant using analysis of covariance with baseline as covariate (p=0.04)
Not significant using analysis of variance (values shown in table)
[b] Statistically significant for insulin (p=0.04)

Table 6. Summary of Mean Changes from Baseline* in HbA_{1c}, Fasting Plasma Glucose, and Body Weight at Final Visit (16-week study)

	GLUCOPHAGE XR					Placebo
	500 mg Once Daily	1000 mg Once Daily	1500 mg Once Daily	2000 mg Once Daily	1000 mg Twice Daily	
Hemoglobin A_{1c} (%)	(n=115)	(n=115)	(n=111)	(n=125)	(n=112)	(n=111)
Baseline	8.2	8.4	8.3	8.4	8.4	8.4
Change at FINAL VISIT	-0.4	-0.6	-0.9	-0.8	-1.1	0.1
p-value[a]	<0.001	<0.001	<0.001	<0.001	<0.001	[illegible]
FPG (mg/dL)	(n=126)	(n=118)	(n=120)	(n=132)	(n=122)	[illegible]
Baseline	182.7	183.7	178.9	181.0	181.6	179.6
Change at FINAL VISIT	-15.2	-19.3	-28.5	-29.9	-33.6	7.6
p-value[a]	<0.001	<0.001	<0.001	<0.001	<0.001	[illegible]
Body Weight (lbs)	(n=125)	(n=119)	(n=117)	(n=131)	(n=119)	[illegible]
Baseline	192.9	191.8	188.3	195.4	192.5	194.3
Change at FINAL VISIT	-1.3	-1.3	-0.7	-1.5	-2.2	-1.8
p-value[a]	NS**	NS**	NS**	NS**	NS**	[illegible]

* All patients on diet therapy at Baseline
[a] All comparisons versus Placebo
**Not statistically significant

Pediatric Clinical Studies

In a double-blind, placebo-controlled study in pediatric patients aged 10 to 16 years with type 2 diabetes (mean FPG 182.2 mg/dL), treatment with GLUCOPHAGE (up to 2000 mg/day) for up to 16 weeks (mean duration of treatment 11 weeks) resulted in a significant mean net reduction in FPG of 64.3 mg/dL, compar[illegible] placebo (see **Table 10**).

Table 10. GLUCOPHAGE vs Placebo (Pediatrics[a]) Summary of Mean Changes from Baseline* in Plasma Glucose and Body Weight at Final Visit

	GLUCOPHAGE	Placebo
FPG (mg/dL)	(n=37)	(n=36)
Baseline	162.4	192.3
Change at FINAL VISIT	-42.9	21.4
Body Weight (lbs)	(n=39)	(n=38)
Baseline	205.3	189.0
Change at FINAL VISIT	-3.3	-2.0

[a] Pediatric patients mean age 13.8 years (range [illegible] years)
* All patients on diet therapy at Baseline
** Not statistically significant

INDICATIONS AND USE

GLUCOPHAGE (metformin hydrochloride tablets) and GLUCOPHAGE XR (metformin hydrochloride extended-release tablets), as monotherapy, are indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes. GLUCOPHAGE is indicated in patients 10 years of age and older, and GLUCOPHAGE XR is indicated in patients 17 years of age and older. GLUCOPHAGE or GLUCOPHAGE XR may be used concomitantly with a sulfonylurea or insulin to improve glycemic control in adults (17 years of age and older).

CONTRAINDICATIONS

GLUCOPHAGE and GLUCOPHAGE XR are contraindicated in patients with:

1. Renal disease or renal dysfunction (e.g., as suggested by serum creatinine levels ≥ 1.5 mg/dL [males], ≥ 1.4 mg/dL [females] or abnormal creatinine clearance) which may also result from conditions such as cardiovascular collapse (shock), acute myocardial infarction, and septicemia (see WARNINGS and PRECAUTIONS).
2. Congestive heart failure requiring pharmacologic treatment.
3. Known hypersensitivity to metformin hydrochloride.
4. Acute or chronic metabolic acidosis, including diabetic ketoacidosis, with or without coma. Diabetic ketoacidosis should be treated with insulin.

GLUCOPHAGE and GLUCOPHAGE XR should be temporarily discontinued in patients undergoing radiologic studies involving intravascular administration of iodinated contrast materials, because use of such products may result in acute alteration of renal function. (See also PRECAUTIONS.)

WARNINGS

Lactic Acidosis

Lactic acidosis is a rare, but serious, metabolic complication that can occur due to metformin accumulation during treatment with GLUCOPHAGE or GLUCOPHAGE XR; when it occurs, it is fatal in approximately 50% of cases. Lactic acidosis may also occur in association with a number of pathophysiologic conditions, including diabetes mellitus, and whenever there is significant tissue hypoperfusion and hypoxemia. Lactic acidosis is characterized by elevated blood lactate levels (>5 mmol/L), decreased blood pH, electrolyte disturbances with an increased anion gap, and an increased lactate/pyruvate ratio. When metformin is implicated as the cause of lactic acidosis, metformin plasma levels >5 µg/mL are generally found.

The reported incidence of lactic acidosis in patients receiving metformin hydrochloride is very low (approximately 0.03 cases/1000 patient-years, with approximately 0.015 fatal cases/1000 patient-years). Reported cases have occurred primarily in diabetic patients with significant renal insufficiency, including both intrinsic renal disease and renal hypoperfusion, often in the setting of multiple concomitant medical/surgical problems and multiple concomitant medications. Patients with congestive heart failure requiring pharmacologic management, in particular, those with unstable or acute congestive heart failure who are at risk of hypoperfusion and hypoxemia, are at increased risk of lactic acidosis. The risk of lactic acidosis increases with the degree of renal dysfunction and the patient's age. The risk of lactic acidosis may, therefore, be significantly decreased by regular monitoring of renal function in patients taking GLUCOPHAGE or GLUCOPHAGE XR and by use of the minimum effective dose of GLUCOPHAGE or GLUCOPHAGE XR. In particular, treatment of the elderly should be accompanied by careful monitoring of renal function. GLUCOPHAGE or GLUCOPHAGE XR treatment should not be initiated in patients ≥ 80 years of age unless measurement of creatinine clearance demonstrates that renal function is not reduced, as these patients are more susceptible to developing lactic acidosis. In addition, GLUCOPHAGE and GLUCOPHAGE XR should be promptly withheld in the presence of any condition associated with hypoxemia, dehydration, or sepsis. Because impaired hepatic function may significantly limit the ability to clear lactate, GLUCOPHAGE and GLUCOPHAGE XR should generally be avoided in patients with clinical or laboratory evidence of hepatic disease. Patients should be cautioned against excessive alcohol intake, either acute or chronic, when taking GLUCOPHAGE or GLUCOPHAGE XR, since alcohol potentiates the effects of metformin hydrochloride on lactate metabolism. In addition, GLUCOPHAGE and GLUCOPHAGE XR should be temporarily discontinued prior to any intravascular radiocontrast study and for any surgical procedure (see also PRECAUTIONS).

The onset of lactic acidosis often is subtle, and accompanied only by nonspecific symptoms such as malaise, myalgias, respiratory distress, increasing somnolence, and nonspecific abdominal distress. There may be associated hypothermia, hypotension, and resistant bradyarrhythmias with more marked acidosis. The patient and the patient's physician must be aware of the possible importance of such symptoms and the patient should be instructed to notify the physician immediately if they occur (see also PRECAUTIONS). GLUCOPHAGE and GLUCOPHAGE XR should be withdrawn until the situation is clarified. Serum electrolytes, ketones, blood glucose and, if indicated, blood pH, lactate levels, and even blood metformin levels may be useful. Once a patient is stabilized on any dose level of GLUCOPHAGE or GLUCOPHAGE XR, gastrointestinal symptoms, which are common during initiation of therapy, are unlikely to be drug related. Later occurrence of gastrointestinal symptoms could be due to lactic acidosis or other serious disease.

Levels of fasting venous plasma lactate above the upper limit of normal but less than 5 mmol/L in patients taking GLUCOPHAGE or GLUCOPHAGE XR do not necessarily indicate impending lactic acidosis and may be explainable by other mechanisms, such as poorly controlled diabetes or obesity, vigorous physical activity, or technical problems in sample handling. (See also PRECAUTIONS.)

Lactic acidosis should be suspected in any diabetic patient with metabolic acidosis lacking evidence of ketoacidosis (ketonuria and ketonemia).

Lactic acidosis is a medical emergency that must be treated in a hospital setting. In a patient with lactic acidosis who is taking GLUCOPHAGE or GLUCOPHAGE XR, the drug should be discontinued immediately and general supportive measures promptly instituted. Because metformin hydrochloride is dialyzable (with a clearance of up to 170 mL/min under good hemodynamic conditions), prompt hemodialysis is recommended to correct the acidosis and remove the accumulated metformin. Such management often results in prompt reversal of symptoms and recovery. (See also CONTRAINDICATIONS and PRECAUTIONS.)

Table 7. Summary of Mean Changes from Baseline* in HbA_{1c}, Fasting Plasma Glucose, and Body Weight at Week 12 and at Final Visit (24-week study)

	GLUCOPHAGE 500 mg Twice Daily	GLUCOPHAGE XR 1000 mg Once Daily	GLUCOPHAGE XR 1500 mg Once Daily
Hemoglobin A_{1c} (%)	(n=67)	(n=72)	(n=66)
Baseline	7.06	6.99	7.02
Change at 12 Weeks	0.14	0.23	0.04
(95% CI)	(-0.03, 0.31)	(0.10, 0.36)	(-0.08, 0.15)
Change at FINAL VISIT	0.14†	0.27	0.13
(95% CI)	(-0.04, 0.31)	(0.11, 0.43)	(-0.02, 0.28)
FPG (mg/dL)	(n=69)	(n=72)	(n=70)
Baseline	127.2	131.0	131.4
Change at 12 Weeks	12.9	9.5	3.7
(95% CI)	(6.5, 19.4)	(4.4, 14.6)	(-0.4, 7.8)
Change at FINAL VISIT	14.0	11.5	7.6
(95% CI)	(7.0, 21.0)	(4.4, 18.6)	(1.0, 14.2)
Body Weight (lbs)	(n=71)	(n=74)	(n=71)
Baseline	210.3	202.8	192.7
Change at 12 Weeks	0.4	0.9	0.7
(95% CI)	(-0.4, 1.5)	(0.0, 2.0)	(-0.4, 1.8)
Change at FINAL VISIT	0.9	1.1	0.9
(95% CI)	(-0.4, 2.2)	(-0.2, 2.4)	(-0.4, 2.0)

*All patients on GLUCOPHAGE 500 mg twice daily at Baseline

†p<0.05

Table 8. Summary of Mean Percent Changes from Baseline* in Major Lipid Variables at Final Visit (16-week study)

	GLUCOPHAGE XR					
	500 mg Once Daily	1000 mg Once Daily	1500 mg Once Daily	2000 mg Once Daily	1000 mg Twice Daily	Placebo
Cholesterol (mg/dL)	(n=120)	(n=113)	(n=110)	(n=126)	(n=117)	(n=110)
Baseline	210.3	218.1	214.6	204.4	208.2	208.6
% change at FINAL VISIT	1.0%	1.7%	0.7%	1.6%	-2.6%	2.6%
Triglycerides (mg/dL)	(n=120)	(n=113)	(n=110)	(n=126)	(n=117)	(n=110)
Baseline	220.2	211.9	198.0	194.2	179.0	211.7
% change at FINAL VISIT	14.5%	9.4%	15.1%	14.9%	9.4%	10.9%
HDL cholesterol (mg/dL)	(n=119)	(n=113)	(n=109)	(n=126)	(n=117)	(n=107)
Baseline	131.0	134.9	135.8	125.8	131.4	131.9
% change at FINAL VISIT	1.4%	-1.6%	-3.5%	-3.3%	-5.5%	3.2%
LDL cholesterol (mg/dL)	(n=120)	(n=108)	(n=108)	(n=125)	(n=117)	(n=108)
Baseline	40.8	41.6	40.6	40.2	42.4	39.4
% change at FINAL VISIT	6.2%	8.6%	5.5%	6.1%	7.1%	5.8%

*All patients on diet therapy at Baseline

PRECAUTIONS

General

Monitoring of renal function — Metformin is known to be substantially excreted by the kidney, and the risk of metformin accumulation and lactic acidosis increases with the degree of impairment of renal function. Thus, patients with serum creatinine levels above the upper limit of normal for their age, should not receive GLUCOPHAGE (metformin hydrochloride tablets) or GLUCOPHAGE XR (metformin hydrochloride extended-release tablets). In patients with advanced age, GLUCOPHAGE and GLUCOPHAGE XR should be carefully titrated to establish the minimum dose for adequate glycemic effect, because aging is associated with reduced renal function. In elderly patients, particularly those ≥80 years of age, renal function should be monitored regularly and, generally, GLUCOPHAGE and GLUCOPHAGE XR should not be titrated to the maximum dose (see WARNINGS and DOSAGE AND ADMINISTRATION).

Before initiation of GLUCOPHAGE or GLUCOPHAGE XR therapy and at least annually thereafter, renal function should be assessed and verified as normal. In patients in whom development of renal dysfunction is anticipated, renal function should be assessed more frequently and GLUCOPHAGE or GLUCOPHAGE XR discontinued if evidence of renal impairment is present.

Continued on next page

Use of concomitant medications that may affect renal function or metformin disposition — Concomitant medication(s) that may affect renal function or result in significant hemodynamic change or may interfere with the disposition of metformin, such as cationic drugs that are eliminated by renal tubular secretion (see **PRECAUTIONS: Drug Interactions**), should be used with caution.

Radiologic studies involving the use of intravascular iodinated contrast materials (for example, intravenous urogram, intravenous cholangiography, angiography, and computed tomography (CT) scans with intravascular contrast materials) — Intravascular contrast studies with iodinated materials can lead to acute alteration of renal function and have been associated with lactic acidosis in patients receiving metformin (see **CONTRAINDICATIONS**). Therefore, in patients in whom any such study is planned, GLUCOPHAGE or GLUCOPHAGE XR should be temporarily discontinued at the time of or prior to the procedure, and withheld for 48 hours subsequent to the procedure and reinstituted only after renal function has been re-evaluated and found to be normal.

Hypoxic states — Cardiovascular collapse (shock), from whatever cause, acute congestive heart failure, acute myocardial infarction and other conditions characterized by hypoxemia have been associated with lactic acidosis and may also cause prerenal azotemia. When such events occur in patients on GLUCOPHAGE or GLUCOPHAGE XR therapy, the drug should be promptly discontinued.

Surgical procedures — GLUCOPHAGE or GLUCOPHAGE XR therapy should be temporarily suspended for any surgical procedure (except minor procedures not associated with restricted intake of food and fluids) and should not be restarted until the patient's oral intake has resumed and renal function has been evaluated as normal.

Alcohol intake — Alcohol is known to potentiate the effect of metformin on lactate metabolism. Patients, therefore, should be warned against excessive alcohol intake, acute or chronic, while receiving GLUCOPHAGE or GLUCOPHAGE XR.

Impaired hepatic function — Since impaired hepatic function has been associated with some cases of lactic acidosis, GLUCOPHAGE and GLUCOPHAGE XR should generally be avoided in patients with clinical or laboratory evidence of hepatic disease.

Vitamin B_{12} levels — In controlled clinical trials of GLUCOPHAGE of 29 weeks duration, a decrease to subnormal levels of previously normal serum Vitamin B_{12} levels, without clinical manifestations, was observed in approximately 7% of patients. Such decrease, possibly due to interference with B_{12} absorption from the B_{12}-intrinsic factor complex, is, however, very rarely, associated with anemia and appears to be rapidly reversible with discontinuation of GLUCOPHAGE or Vitamin B_{12} supplementation. Measurement of hematologic parameters on an annual basis is advised in patients on GLUCOPHAGE or GLUCOPHAGE XR and any apparent abnormalities should be appropriately investigated and managed (see **PRECAUTIONS: Laboratory Tests**).

Certain individuals (those with inadequate Vitamin B_{12} or calcium intake or absorption) appear to be predisposed to developing subnormal Vitamin B_{12} levels. In these patients, routine serum Vitamin B_{12} measurements at two- to three-year intervals may be useful.

Change in clinical status of patients with previously controlled type 2 diabetes — A patient with type 2 diabetes previously well controlled on GLUCOPHAGE or GLUCOPHAGE XR who develops laboratory abnormalities or clinical illness (especially vague and poorly defined illness) should be evaluated promptly for evidence of ketoacidosis or lactic acidosis. Evaluation should include serum electrolytes and ketones, blood glucose and, if indicated, blood pH, lactate, pyruvate, and metformin levels. If acidosis of either form occurs, GLUCOPHAGE or GLUCOPHAGE XR must be stopped immediately and other appropriate corrective measures initiated (see also **WARNINGS**).

Hypoglycemia — Hypoglycemia does not occur in patients receiving GLUCOPHAGE or GLUCOPHAGE XR alone under usual circumstances of use, but could occur when caloric intake is deficient, when strenuous exercise is not compensated by caloric supplementation, or during concomitant use with other glucose-lowering agents (such as sulfonylureas and insulin) or ethanol.

Elderly, debilitated, or malnourished patients, and those with adrenal or pituitary insufficiency or alcohol intoxication are particularly susceptible to hypoglycemic effects. Hypoglycemia may be difficult to recognize in the elderly, and in people who are taking beta-adrenergic blocking drugs.

Loss of control of blood glucose — When a patient stabilized on any diabetic regimen is exposed to stress such as fever, trauma, infection, or surgery, a temporary loss of glycemic control may occur. At such times, it may be necessary to withhold GLUCOPHAGE or GLUCOPHAGE XR and temporarily administer insulin. GLUCOPHAGE or GLUCOPHAGE XR may be reinstituted after the acute episode is resolved.

The effectiveness of oral antidiabetic drugs in lowering blood glucose to a targeted level decreases in many patients over a period of time. This phenomenon, which may be due to progression of the underlying disease or to diminished responsiveness to the drug, is known as secondary failure, to distinguish it from primary failure in which the drug is ineffective during initial therapy. Should secondary failure occur with either GLUCOPHAGE or GLUCOPHAGE XR or sulfonylurea monotherapy, combined therapy with GLUCOPHAGE or GLUCOPHAGE XR and sulfonylurea may result in a response. Should secondary failure occur with combined GLUCOPHAGE/sulfonylurea therapy or GLUCOPHAGE XR/sulfonylurea therapy, it may be necessary to consider therapeutic alternatives including initiation of insulin therapy.

Information for Patients

Patients should be informed of the potential risks and benefits of GLUCOPHAGE or GLUCOPHAGE XR and of alternative modes of therapy. They should also be informed about the importance of adherence to dietary instructions, of a regular exercise program, and of regular testing of blood glucose, glycosylated hemoglobin, renal function, and hematologic parameters.

The risks of lactic acidosis, its symptoms, and conditions that predispose to its development, as noted in the **WARNINGS** and **PRECAUTIONS** sections, should be explained to patients. Patients should be advised to discontinue GLUCOPHAGE or GLUCOPHAGE XR immediately and to promptly notify their health practitioner if unexplained hyperventilation, myalgia, malaise, unusual somnolence, or other nonspecific symptoms occur. Once a patient is stabilized on any dose level of GLUCOPHAGE or GLUCOPHAGE XR, gastrointestinal symptoms, which are common during initiation of metformin therapy, are unlikely to be drug related. Later occurrence of gastrointestinal symptoms could be due to lactic acidosis or other serious disease.

Patients should be counselled against excessive alcohol intake, either acute or chronic, while receiving GLUCOPHAGE or GLUCOPHAGE XR.

GLUCOPHAGE (metformin hydrochloride tablets) or GLUCOPHAGE XR (metformin hydrochloride extended-release tablets) alone does not usually cause hypoglycemia, although it may occur when GLUCOPHAGE or GLUCOPHAGE XR is used in conjunction with oral sulfonylureas and insulin. When initiating combination therapy, the risks of hypoglycemia, its symptoms and treatment, and conditions that predispose to its development should be explained to patients and responsible family members.

(See **Patient Information** Printed Below.)

Laboratory Tests

Response to all diabetic therapies should be monitored by periodic measurements of fasting blood glucose and glycosylated hemoglobin levels, with a goal of decreasing these levels toward the normal range. During initial dose titration, fasting glucose can be used to determine the therapeutic response. Thereafter, both glucose and glycosylated hemoglobin should be monitored. Measurements of glycosylated hemoglobin may be especially useful for evaluating long-term control (see also **DOSAGE AND ADMINISTRATION**).

Initial and periodic monitoring of hematologic parameters (e.g., hemoglobin/hematocrit and red blood cell indices) and renal function (serum creatinine) should be performed, at least on an annual basis. While megaloblastic anemia has rarely been seen with GLUCOPHAGE therapy, if this is suspected, Vitamin B_{12} deficiency should be excluded.

Drug Interactions (clinical evaluation of drug interactions done with GLUCOPHAGE)

Glyburide — In a single-dose interaction study in type 2 diabetes patients, co-administration of metformin and glyburide did not result in any changes in either metformin pharmacokinetics or pharmacodynamics. Decreases in glyburide AUC and C_{max} were observed, but were highly variable. The single-dose nature of this study and the lack of correlation between glyburide blood levels and pharmacodynamic effects, makes the clinical significance of this interaction uncertain (see **DOSAGE AND ADMINISTRATION: Concomitant GLUCOPHAGE or GLUCOPHAGE XR and Oral Sulfonylurea Therapy**).

Furosemide — A single-dose, metformin-furosemide drug interaction study in healthy subjects demonstrated that pharmacokinetic parameters of both compounds were affected by co-administration. Furosemide increased the metformin plasma and blood C_{max} by 22% and blood AUC by 15%, without any significant change in metformin renal clearance. When administered with metformin, the C_{max} and AUC of furosemide were 31% and 12% smaller, respectively, than when administered alone, and the terminal half-life was decreased by 32%, without any significant change in furosemide renal clearance. No information is available about the interaction of metformin and furosemide when co-administered chronically.

Nifedipine — A single-dose, metformin-nifedipine drug interaction study in normal healthy volunteers demonstrated that co-administration of nifedipine increased plasma metformin C_{max} and AUC by 20% and 9%, respectively, and increased the amount excreted in the urine. T_{max} and half-life were unaffected. Nifedipine appears to enhance the absorption of metformin. Metformin had minimal effects on nifedipine.

Cationic drugs — Cationic drugs (e.g., amiloride, digoxin, morphine, procainamide, quinidine, quinine, ranitidine, triamterene, trimethoprim, or vancomycin) that are eliminated by renal tubular secretion theoretically have the potential for interaction with metformin by competing for common renal tubular transport systems. Such interaction between metformin and oral cimetidine has been observed in normal healthy volunteers in both single- and multiple-dose, metformin-cimetidine drug interaction studies, with 60% increase in peak metformin plasma and whole blood concentrations and a 40% increase in plasma and whole blood metformin AUC. There was no change in elimination half-life in the single-dose study. Metformin had no effect on cimetidine pharmacokinetics. Although such interactions remain theoretical (except for cimetidine), careful patient monitoring and dose adjustment of GLUCOPHAGE or GLUCOPHAGE XR and/or the interfering drug is recommended in patients who are taking cationic medications that are excreted via the proximal renal tubular secretory system.

Other — Certain drugs tend to produce hyperglycemia and may lead to loss of glycemic control. These drugs include the thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blocking drugs, and isoniazid. When such drugs are administered to a patient receiving GLUCOPHAGE or GLUCOPHAGE XR, the patient should be closely observed for loss of blood glucose control. When such drugs are withdrawn from a patient receiving GLUCOPHAGE or GLUCOPHAGE XR, the patient should be observed closely for hypoglycemia.

In healthy volunteers, the pharmacokinetics of metformin and propranolol, and metformin and ibuprofen were not affected when co-administered in single-dose interaction studies.

Metformin is negligibly bound to plasma proteins and is, therefore, less likely to interact with highly protein-bound drugs such as salicylates, sulfonamides, chloramphenicol, and probenecid, as compared to the sulfonylureas, which are extensively bound to serum proteins.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term carcinogenicity studies have been performed in rats (dosing duration of 104 weeks) and mice (dosing duration of 91 weeks) at doses up to and including 900 mg/kg/day and 1500 mg/kg/day, respectively. These doses are both approximately four times the maximum recommended human daily dose of 2000 mg based on body surface area comparisons. No evidence of carcinogenicity with metformin was found in either male or female mice. Similarly, there was no tumorigenic potential observed with metformin in male rats. There was, however, an increased incidence of benign stromal uterine polyps in female rats treated with 900 mg/kg/day.

There was no evidence of mutagenic potential of metformin in the following *in vitro* tests: Ames test (*S. typhimurium*), gene mutation test (mouse lymphoma cells), or chromosomal aberrations test (human lymphocytes). Results in the *in vivo* mouse micronucleus test were also negative.

Fertility of male or female rats was unaffected by metformin when administered at doses as high as 600 mg/kg/day, which is approximately three times the maximum recommended human daily dose based on body surface area comparisons.

Pregnancy

Teratogenic Effects: Pregnancy Category B.

Recent information strongly suggests that abnormal blood glucose levels during pregnancy are associated with a higher incidence of congenital abnormalities. Most experts recommend that insulin be used during pregnancy to maintain blood glucose levels as close to normal as possible. Because animal reproduction studies are not always predictive of human response, GLUCOPHAGE and GLUCOPHAGE XR should not be used during pregnancy unless clearly needed.

There are no adequate and well-controlled studies in pregnant women with GLUCOPHAGE or GLUCOPHAGE XR. Metformin was not teratogenic in rats and rabbits at doses up to 600 mg/kg/day. This represents an exposure of about two and six times the maximum recommended human daily dose of 2000 mg based on body surface area comparisons in rats and rabbits, respectively. Determination of fetal concentrations demonstrated a partial placental barrier to metformin.

Nursing Mothers

Studies in lactating rats show that metformin is excreted into milk and reaches levels comparable to those in plasma. Similar studies have not been conducted in nursing mothers. Because the potential for hypoglycemia in nursing infants may exist, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. If GLUCOPHAGE or GLUCOPHAGE XR is discontinued and if diet alone is inadequate for controlling blood glucose, insulin therapy should be considered.

Pediatric Use

The safety and effectiveness of GLUCOPHAGE for the treatment of type 2 diabetes have been established in pediatric patients ages 10 to 16 years (studies have not been conducted in pediatric patients below the age of 10 years). Use of GLUCOPHAGE in this age group is supported by evidence from adequate and well-controlled studies of GLUCOPHAGE in adults with additional data from a controlled clinical study in pediatric patiens ages 10-16 years with type 2 diabetes, which demonstrated a similar response in glycemic control to that seen in adults (see **CLINICAL PHARMACOLOGY: Pediatric Clinical Studies**.) In this study, adverse effects were similar to those described in adults. (See **ADVERSE REACTIONS: Pediatric Patients**.) A maximum daily dose of 2000 mg is recommended. (See **DOSAGE AND ADMINISTRATION: Recommended Dosing Schedule: Pediatrics**.)

Hemic and Lymphatic Systems: Anemia, including hemolytic anemia, thrombocytopenia, thrombocytopenic purpura, eosinophilia, leukopenia and agranulocytosis have been reported during therapy with penicillins. These reactions are usually reversible on discontinuation of therapy and are believed to be hypersensitivity phenomena. A slight thrombocytosis was noted in less than 1% of the patients treated with *Augmentin*. There have been reports of increased prothrombin time in patients receiving *Augmentin* and anticoagulant therapy concomitantly.

Central Nervous System: Agitation, anxiety, behavioral changes, confusion, convulsions, dizziness, insomnia, and reversible hyperactivity have been reported rarely.

Miscellaneous: Tooth discoloration has been reported very rarely in children. Good oral hygiene may help to prevent tooth discoloration as it can usually be removed by brushing.

OVERDOSAGE

Following overdosage, patients have experienced primarily gastrointestinal symptoms including stomach and abdominal pain, vomiting, and diarrhea. Rash, hyperactivity, or drowsiness have also been observed in a small number of patients.

In the case of overdosage, discontinue *Augmentin ES-600*, treat symptomatically, and institute supportive measures as required. If the overdosage is very recent and there is no contraindication, an attempt at emesis or other means of removal of drug from the stomach may be performed. A prospective study of 51 pediatric patients at a poison control center suggested that overdosages of less than 250 mg/kg of amoxicillin are not associated with significant clinical symptoms and do not require gastric emptying.[4]

Interstitial nephritis resulting in oliguric renal failure has been reported in a small number of patients after overdosage with amoxicillin. Renal impairment appears to be reversible with cessation of drug administration. High blood levels may occur more readily in patients with impaired renal function because of decreased renal clearance of both amoxicillin and clavulanate. Both amoxicillin and clavulanate are removed from the circulation by hemodialysis.

DOSAGE AND ADMINISTRATION

***Augmentin ES-600*, 600 mg/5 mL, does not contain the same amount of clavulanic acid (as the potassium salt) as any of the other *Augmentin* suspensions. *Augmentin ES-600* contains 42.9 mg of clavulanic acid per 5 mL whereas *Augmentin* 200 mg/5 mL suspension contains 28.5 mg of clavulanic acid per 5 mL and the 400 mg/5 mL suspension contains 57 mg of clavulanic acid per 5 mL. Therefore, the *Augmentin* 200 mg/5 mL and 400 mg/5 mL suspensions should *not* be substituted for *Augmentin ES-600*, as they are not interchangeable.**

Dosage:

Pediatric patients 3 months and older: Based on the amoxicillin component (600 mg/5 mL), the recommended dose of *Augmentin ES-600* is 90 mg/kg/day divided every 12 hours, administered for 10 days (see chart below).

Body Weight (kg)	Volume of *Augmentin ES-600* providing 90 mg/kg/day
8	3.0 mL twice daily
12	4.5 mL twice daily
16	6.0 mL twice daily
20	7.5 mL twice daily
24	9.0 mL twice daily
28	10.5 mL twice daily
32	12.0 mL twice daily
36	13.5 mL twice daily

Pediatric patients weighing 40 kg and more: Experience with *Augmentin ES-600* (600 mg/5 mL formulation) in this group is not available.

Adults: Experience with *Augmentin ES-600* (600 mg/5 mL formulation) in adults is not available and adults who have difficulty swallowing should not be given *Augmentin ES-600* (600 mg/5 mL) in place of the *Augmentin* 500 mg or 875 mg tablet.

Hepatically impaired patients should be dosed with caution and hepatic function monitored at regular intervals. (See WARNINGS.)

DIRECTIONS FOR MIXING ORAL SUSPENSION

Prepare a suspension at time of dispensing as follows: Tap bottle until all the powder flows freely. Add approximately 2/3 of the total amount of water for reconstitution (see table below) and shake vigorously to suspend powder. Add remainder of the water and again shake vigorously.

(600 mg/5 mL Suspension)

Bottle Size	Amount of Water Required for Suspension
50 mL	45 mL
75 mL	65 mL
100 mL	90 mL
150 mL	130 mL

Each teaspoonful (5 mL) will contain 600 mg amoxicillin as the trihydrate and 42.9 mg of clavulanic acid as the potassium salt.

Note: SHAKE ORAL SUSPENSION WELL BEFORE USING.

Administration: To minimize the potential for gastrointestinal intolerance, *Augmentin ES-600* should be taken at the start of a meal. Absorption of clavulanate potassium may be enhanced when *Augmentin ES-600* is administered at the start of a meal.

HOW SUPPLIED

***AUGMENTIN ES-600*, 600 MG/5 ML, FOR ORAL SUSPENSION:** Each 5 mL of reconstituted orange-raspberry-flavored suspension contains 600 mg amoxicillin and 42.9 mg clavulanic acid as the potassium salt.

NDC 0029-6094-29 ..... 50 mL bottle
NDC 0029-6094-39 ..... 75 mL bottle
NDC 0029-6094-51 ..... 100 mL bottle
NDC 0029-6094-22 ..... 150 mL bottle

STORAGE

Store reconstituted suspension under refrigeration. Discard unused suspension after 10 days. Store dry powder for oral suspension at or below 25°C (77°F). Dispense in original container.

Description of Clinical Studies

Two clinical studies were conducted in pediatric patients with acute otitis media.

A non-comparative, open-label study assessed the bacteriologic and clinical efficacy of *Augmentin ES-600* (90/6.4 mg/kg/day, divided every 12 hours) for 10 days in 521 pediatric patients (ages 3 to 50 months) with acute otitis media. The primary objective was to assess bacteriological response in children with acute otitis media due to *S. pneumoniae* with amoxicillin/clavulanic acid MICs of 4 µg/mL. The study sought the enrollment of patients with the following risk factors: failure of antibiotic therapy for acute otitis media in the previous 3 months, history of recurrent episodes of acute otitis media, ≤2 years of age, or daycare attendance. Prior to receiving *Augmentin ES-600*, all patients had tympanocentesis to obtain middle ear fluid for bacteriological evaluation. Patients from whom *S. pneumoniae* (alone or in combination with other bacteria) was isolated had a second tympanocentesis 4 to 6 days after the start of therapy. Clinical assessments were planned for all patients during treatment (4-6 days after starting therapy), as well as 2-4 days post-treatment and 15-18 days post-treatment. Bacteriological success was defined as the absence of the pretreatment pathogen from the on therapy tympanocentesis specimen. Clinical success was defined as improvement or resolution of signs and symptoms. Clinical failure was defined as lack of improvement or worsening of signs and/or symptoms at any time following at least 72 hours of Augmentin ES-600 (amoxicillin/clavulanate potassium); patients who received an additional systemic antibacterial drug for otitis media after 3 days of therapy were considered clinical failures. Bacteriological eradication on therapy (day 4-6 visit) in the per protocol population is summarized in the following table:

[See table 3 at top of previous page]

Clinical assessments were made in the per protocol population 2-4 days post-therapy and 15-18 days post-therapy. Patients who responded to therapy 2-4 days post-therapy were followed for 15-18 days post-therapy to assess them for acute otitis media. Nonresponders at 2-4 days post-therapy were considered failures at the latter timepoint.

[See table 4 on previous page]

In the intent-to-treat analysis, overall clinical outcomes at 2-4 days and 15-18 days post-treatment in patients with *S. pneumoniae* with penicillin MIC = 2 µg/mL and 4 µg/mL were 29/41 (71%) and 17/41 (41.5%), respectively.

In the intent-to-treat population of 521 patients, the most frequently reported adverse events were vomiting (6.9%), fever (6.1%), contact dermatitis (i.e., diaper rash) (6.1%), upper respiratory tract infection (4.0%), and diarrhea (3.8%). Protocol-defined diarrhea (i.e., three or more watery stools in one day or two watery stools per day for two consecutive days as recorded on diary cards) occurred in 12.9% of patients.

A double-blind, randomized, clinical study, compared *Augmentin ES-600* (90/6.4 mg/kg/day, divided every 12 hours) to *Augmentin* (45/6.4 mg/kg/day, divided every 12 hours) for 10 days in 450 pediatric patients (ages 3 months to 12 years) with acute otitis media. The primary objective of the study was to compare the safety of *Augmentin ES-600* to *Augmentin*. There was no statistically significant difference between treatments in the proportion of patients with one or more adverse events. The most frequently reported adverse events for *Augmentin ES-600* and the *Augmentin* comparator were coughing (11.9% vs. 6.8%), vomiting (6.5% vs. 7.7%), contact dermatitis (i.e., diaper rash, 6.0% vs. 4.8%), fever (5.5% vs. 3.9%), and upper respiratory infection (3.0% vs. 9.2%), respectively. The frequencies of protocol-defined diarrhea with *Augmentin ES-600* (11.1%) and *Augmentin* (9.4%) were similar (95% confidence interval on difference: −4.2% to 7.7%). Only 2 patients in *Augmentin ES-600* group and 1 patient in *Augmentin* group were withdrawn due to diarrhea.

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GlaxoSmithKline, Research Triangle Park, NC 27709

June 2001/AE:L1

AVANDIA®

[ə-van'dē-ə]

brand of rosiglitazone maleate tablets

DESCRIPTION

Avandia (rosiglitazone maleate) is an oral antidiabetic agent which acts primarily by increasing insulin sensitivity. *Avandia* is used in the management of type 2 diabetes mellitus (also known as non-insulin-dependent diabetes mellitus [NIDDM] or adult-onset diabetes). *Avandia* improves glycemic control while reducing circulating insulin levels. Pharmacological studies in animal models indicate that rosiglitazone improves sensitivity to insulin in muscle and adipose tissue and inhibits hepatic gluconeogenesis. Rosiglitazone maleate is not chemically or functionally related to the sulfonylureas, the biguanides, or the alpha-glucosidase inhibitors.

Chemically, rosiglitazone maleate is (±)-5-[[4-[2-(methyl-2-pyridinylamino)ethoxy]phenyl]methyl]-2,4-thiazolidinedione, (*Z*)-2-butenedioate (1:1) with a molecular weight of 473.52 (357.44 free base). The molecule has a single chiral center and is present as a racemate. Due to rapid interconversion, the enantiomers are functionally indistinguishable. The molecular formula is $C_{18}H_{19}N_3O_3S{\cdot}C_4H_4O_4$. Rosiglitazone maleate is a white to off-white solid with a melting point range of 122° to 123°C. The pKa values of rosiglitazone maleate are 6.8 and 6.1. It is readily soluble in ethanol and a buffered aqueous solution with pH of 2.3; solubility decreases with increasing pH in the physiological range.

Each pentagonal film-coated Tiltab® tablet contains rosiglitazone maleate equivalent to rosiglitazone, 2 mg, 4 mg, or 8 mg, for oral administration. Inactive ingredients are: hydroxypropyl methylcellulose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol 3000, sodium starch glycolate, titanium dioxide, triacetin, and one or more of the following: synthetic red and yellow iron oxides and talc.

CLINICAL PHARMACOLOGY

Mechanism of Action

Rosiglitazone, a member of the thiazolidinedione class of antidiabetic agents, improves glycemic control by improving insulin sensitivity. Rosiglitazone is a highly selective and potent agonist for the peroxisome proliferator-activated receptor-gamma (PPARγ). In humans, PPAR receptors are found in key target tissues for insulin action such as adipose tissue, skeletal muscle, and liver. Activation of PPARγ nuclear receptors regulates the transcription of insulin responsive genes involved in the control of glucose production, transport, and utilization. In addition, PPARγ-responsive genes also participate in the regulation of fatty acid metabolism.

Insulin resistance is a common feature characterizing the pathogenesis of type 2 diabetes. The antidiabetic activity of rosiglitazone has been demonstrated in animal models of type 2 diabetes in which hyperglycemia and/or impaired glucose tolerance is a consequence of insulin resistance in target tissues. Rosiglitazone reduces blood glucose concentrations and reduces hyperinsulinemia in the ob/ob obese mouse, db/db diabetic mouse, and fa/fa fatty Zucker rat. In animal models, rosiglitazone's antidiabetic activity is shown to be mediated by increased sensitivity to insulin action in the liver, muscle, and adipose tissues. The expression of the insulin-regulated glucose transporter GLUT4 was increased in adipose tissue. Rosiglitazone did not induce hypoglycemia in animal models of type 2 diabetes and/or impaired glucose tolerance.

Pharmacokinetics and Drug Metabolism

Maximum plasma concentration (C_{max}) and the area under the curve (AUC) of rosiglitazone increase in a dose-proportional manner over the therapeutic dose range (Table 1). The elimination half-life is 3 to 4 hours and is independent of dose.

(SD) Pharmacokinetic Parameters for ...one Following Single Oral Doses (N=32)

	1 mg Fasting	2 mg Fasting	8 mg Fasting	8 mg Fed
...ue	358	733	2971	2890
...hr/mL)	(112)	(184)	(730)	(795)
...hr/mL	76	156	598	432
...ng/mL)	(13)	(42)	(117)	(92)
...hr)	3.16	3.15	3.37	3.59
...life (hr)	(0.72)	(0.39)	(0.63)	(0.70)
...L/hr/kg)	3.03	2.89	2.85	2.97
...ean)	(0.87)	(0.71)	(0.69)	(0.81)

...CL/F = Oral Clearance

...ption:

The absolute bioavailability of rosiglitazone is 99%. Peak plasma concentrations are observed about 1 hour after dosing. Administration of rosiglitazone with food resulted in no change in overall exposure (AUC), but there was an approximately 28% decrease in C_{max} and a delay in T_{max} (1.75 hours). These changes are not likely to be clinically significant; therefore, Avandia (rosiglitazone maleate) may be administered with or without food.

...bution:

The mean (CV%) oral volume of distribution (Vss/F) of rosiglitazone is approximately 17.6 (30%) liters, based on a population pharmacokinetic analysis. Rosiglitazone is approximately 99.8% bound to plasma proteins, primarily albumin.

...olism:

Rosiglitazone is extensively metabolized with no unchanged drug excreted in the urine. The major routes of metabolism are N-demethylation and hydroxylation, followed by conjugation with sulfate and glucuronic acid. All the circulating metabolites are considerably less potent than parent and, therefore, are not expected to contribute to the insulin-sensitizing activity of rosiglitazone.

In vitro data demonstrate that rosiglitazone is predominantly metabolized by Cytochrome P_{450} (CYP) isoenzyme 2C8, with CYP2C9 contributing as a minor pathway.

...etion:

Following oral or intravenous administration of [^{14}C]rosiglitazone maleate, approximately 64% and 23% of the dose was eliminated in the urine and in the feces, respectively. The plasma half-life of [^{14}C]related material ranged from 100 to 158 hours.

Population Pharmacokinetics in Patients with Type 2 Diabetes:

Population pharmacokinetic analyses from three large clinical trials including 642 men and 405 women with type 2 diabetes (aged 35 to 80 years) showed that the pharmacokinetics of rosiglitazone are not influenced by age, race, smoking, or alcohol consumption. Both oral clearance (CL/F) and oral steady-state volume of distribution (Vss/F) were shown to increase with increases in body weight. Over the weight range observed in these analyses (50 to 150 kg), the range of predicted CL/F and Vss/F values varied by <1.7-fold and <2.3-fold respectively. Additionally, rosiglitazone CL/F was shown to be influenced by both weight and gender, being lower (about 15%) in female patients.

Special Populations

Age: Results of the population pharmacokinetic analysis (n=716 <65 years; n=331 ≥65 years) showed that age does not significantly affect the pharmacokinetics of rosiglitazone.

Gender: Results of the population pharmacokinetics analysis showed that the mean oral clearance of rosiglitazone in female patients (n=405) was approximately 6% lower compared to male patients of the same body weight (n=642).

As monotherapy and in combination with metformin, *Avandia* improved glycemic control in both males and females. In metformin combination studies, efficacy was demonstrated with no gender differences in glycemic response. In monotherapy studies, a greater therapeutic response was observed in females; however, in more obese patients, gender differences were less evident. For a given body mass index (BMI), females tend to have a greater fat mass than males. Since the molecular target PPARγ is expressed in adipose tissues, this differentiating characteristic may account, at least in part, for the greater response to *Avandia* in females. Since therapy should be individualized, no dose adjustments are necessary based on gender alone.

Hepatic Impairment: Unbound oral clearance of rosiglitazone was significantly lower in patients with moderate to severe liver disease (Child-Pugh Class B/C) compared to healthy subjects. As a result, unbound C_{max} and AUC were increased 2- and 3-fold, respectively. Elimination half-life for rosiglitazone was about 2 hours longer in patients with liver disease, compared to healthy subjects. Therapy with Avandia (rosiglitazone maleate) should not be initiated if the patient exhibits clinical evidence of active liver disease or increased serum transaminase levels (ALT >2.5X upper limit of normal) at baseline (see PRECAUTIONS, *Hepatic Effects*).

Renal Impairment: There are no clinically relevant differences in the pharmacokinetics of rosiglitazone in patients with mild to severe renal impairment or in hemodialysis-dependent patients compared to subjects with normal renal function. No dosage adjustment is therefore required in such patients receiving *Avandia*. Since metformin is contraindicated in patients with renal impairment, co-administration of metformin with *Avandia* is contraindicated in these patients.

Race: Results of a population pharmacokinetic analysis including subjects of Caucasian, black, and other ethnic origins indicate that race has no influence on the pharmacokinetics of rosiglitazone.

Pediatric Use: The safety and effectiveness of *Avandia* in pediatric patients have not been established.

CLINICAL STUDIES

In clinical studies, treatment with *Avandia* resulted in an improvement in glycemic control, as measured by fasting plasma glucose (FPG) and hemoglobin A1c (HbA1c), with a concurrent reduction in insulin and C-peptide. Postprandial glucose and insulin were also reduced. This is consistent with the mechanism of action of *Avandia* as an insulin sensitizer. The improvement in glycemic control was durable, with maintenance of effect for 52 weeks. The maximum recommended daily dose is 8 mg. Dose-ranging studies suggested that no additional benefit was obtained with a total daily dose of 12 mg.

The addition of *Avandia* to either metformin or a sulfonylurea resulted in significant reductions in hyperglycemia compared to any of these agents alone. These results are consistent with an additive effect on glycemic control when *Avandia* is used as combination therapy.

Patients with lipid abnormalities were not excluded from clinical trials of *Avandia*. In all 26-week controlled trials across the recommended dose range, *Avandia* as monotherapy was associated with increases in total cholesterol, LDL, and HDL and decreases in free fatty acids. These changes were statistically significantly different from placebo or glyburide controls (Table 2).

Increases in LDL occurred primarily during the first 1 to 2 months of therapy with *Avandia* and LDL levels remained elevated above baseline throughout the trials. In contrast, HDL continued to rise over time. As a result, the LDL/HDL ratio peaked after 2 months of therapy and then appeared to decrease over time. Because of the temporal nature of lipid changes, the 52-week glyburide-controlled study is most pertinent to assess long-term effects on lipids. At baseline, week 26, and week 52, mean LDL/HDL ratios were 3.1, 3.2, and 3.0, respectively, for *Avandia* 4 mg twice daily. The corresponding values for glyburide were 3.2, 3.1, and 2.9. The differences in change from baseline between *Avandia* and glyburide at week 52 were statistically significant.

The pattern of LDL and HDL changes following therapy with *Avandia* in combination with other hypoglycemic agents were generally similar to those seen with *Avandia* in monotherapy.

The changes in triglycerides during therapy with Avandia (rosiglitazone maleate) were variable and were generally not statistically different from placebo or glyburide controls.

[See table 2 at top of page]

Table 2: Summary of Mean Lipid Changes in 26-Week Placebo-Controlled and 52-Week Glyburide-Controlled Monotherapy Studies

	Placebo-controlled Studies Week 26			Glyburide-controlled Study Week 26 and Week 52			
		Avandia		Glyburide titration		*Avandia* 8 mg	
	Placebo	4 mg daily*	8 mg daily*	Wk 26	Wk 52	Wk 26	Wk 52
Free Fatty Acids							
N	207	428	436	181	168	166	145
Baseline (mean)	18.1	17.5	17.9	26.4	26.4	26.9	26.6
% Change from baseline (mean)	+0.2%	−7.8%	−14.7%	−2.4%	−4.7%	−20.8%	−21.5%
LDL							
N	190	400	374	175	160	161	133
Baseline (mean)	123.7	126.8	125.3	142.7	141.9	142.1	142.1
% Change from baseline (mean)	+4.8%	+14.1%	+18.6%	−0.9%	−0.5%	+11.9%	+12.1%
HDL							
N	208	429	436	184	170	170	145
Baseline (mean)	44.1	44.4	43.0	47.2	47.7	48.4	48.3
% Change from baseline (mean)	+8.0%	+11.4%	+14.2%	+4.3%	+8.7%	+14.0%	+18.5%

*Once daily and twice daily dosing groups were combined.

Table 3: Glycemic Parameters in Two 26-Week Placebo-Controlled Trials

	Placebo	*Avandia* 2 mg twice daily	*Avandia* 4 mg twice daily
STUDY A			
N	158	166	169
FPG (mg/dL)			
Baseline (mean)	229	227	220
Change from baseline (mean)	19	−38	−54
Difference from placebo (adjusted mean)		−58*	−76*
Responders (≥30 mg/dL decrease from baseline)	16%	54%	64%
HbA1c (%)			
Baseline (mean)	9.0	9.0	8.8
Change from baseline (mean)	0.9	−0.3	−0.6
Difference from placebo (adjusted mean)		−1.2*	−1.5*
Responders (≥0.7% decrease from baseline)	6%	40%	42%

	Placebo	*Avandia* 4 mg once daily	*Avandia* 2 mg twice daily	*Avandia* 8 mg once daily	*Avandia* 4 mg twice daily
STUDY B					
N	173	180	186	181	187
FPG (mg/dL)					
Baseline (mean)	225	229	225	228	228
Change from baseline (mean)	8	−25	−35	−42	−55
Difference from placebo (adjusted mean)	–	−31*	−43*	−49*	−62*
Responders (≥30 mg/dL decrease from baseline)	19%	45%	54%	58%	70%
HbA1c (%)					
Baseline (mean)	8.9	8.9	8.9	8.9	9.0
Change from baseline (mean)	0.8	0.0	−0.1	−0.3	−0.7
Difference from placebo (adjusted mean)	–	−0.8*	−0.9*	−1.1*	−1.5*
Responders (≥0.7% decrease from baseline)	9%	28%	29%	39%	54%

*<0.0001 compared to placebo.

Continued on next page

This product information is based on labeling in effect on July 13, 2001. Further information is available at: GlaxoSmithKline, PO Box 13398, Research Triangle Park, NC 27709, 1-888-825-5249; Corporate Web Site: www.gsk.com

Avandia—Cont.

Monotherapy

A total of 2315 patients with type 2 diabetes, previously treated with diet alone or antidiabetic medication(s), were treated with *Avandia* as monotherapy in six double-blind studies, which included two 26-week placebo-controlled studies, one 52-week glyburide-controlled study, and three placebo-controlled dose-ranging studies of 8 to 12 weeks duration. Previous antidiabetic medication(s) were withdrawn and patients entered a 2 to 4 week placebo run-in period prior to randomization.

Two 26-week, double-blind, placebo-controlled trials, in patients with type 2 diabetes with inadequate glycemic control (mean baseline FPG approximately 228 mg/dL and mean baseline HbA1c 8.9%), were conducted. Treatment with *Avandia* produced statistically significant improvements in FPG and HbA1c compared to baseline and relative to placebo (Table 3).

[See table 3 on previous page]

When administered at the same total daily dose, *Avandia* was generally more effective in reducing FPG and HbA1c when administered in divided doses twice daily compared to once daily doses. However, for HbA1c, the difference between the 4 mg once daily and 2 mg twice daily doses was not statistically significant.

Long-term maintenance of effect was evaluated in a 52-week, double-blind, glyburide-controlled trial in patients with type 2 diabetes. Patients were randomized to treatment with Avandia (rosiglitazone maleate) 2 mg twice daily (N=195) or *Avandia* 4 mg twice daily (N=189) or glyburide (N=202) for 52 weeks. Patients receiving glyburide were given an initial dosage of either 2.5 mg/day or 5.0 mg/day. The dosage was then titrated in 2.5 mg/day increments over the next 12 weeks, to a maximum dosage of 15.0 mg/day in order to optimize glycemic control. Thereafter the glyburide dose was kept constant.

The median titrated dose of glyburide was 7.5 mg. All treatments resulted in a statistically significant improvement in glycemic control from baseline (Figures 1 and 2). At the end of week 52, the reduction from baseline in FPG and HbA1c was –40.8 mg/dL and –0.53% with *Avandia* 4 mg twice daily; –25.4 mg/dL and –0.27% with *Avandia* 2 mg twice daily; and –30.0 mg/dL and –0.72% with glyburide. For HbA1c, the difference between *Avandia* 4 mg twice daily and glyburide was not statistically significant at week 52. The initial fall in FPG with glyburide was greater than with *Avandia*; however, this effect was less durable over time. The improvement in glycemic control seen with *Avandia* 4 mg twice daily at week 26 was maintained through week 52 of the study.

Figure 1: Mean FPG Over Time in a 52-Week Glyburide-Controlled Study

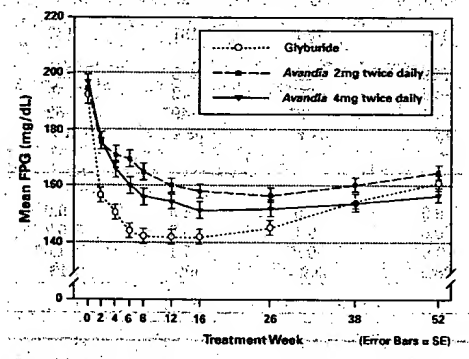
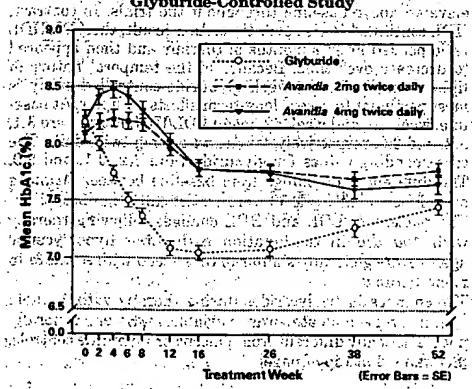


Figure 2. Mean HbA1c Over Time in a 52-Week Glyburide-Controlled Study



Hypoglycemia was reported in 12.1% of glyburide-treated patients versus 0.5% (2 mg twice daily) and 1.6% (4 mg twice daily) of patients treated with *Avandia*. The improvements in glycemic control were associated with a mean weight gain of 1.75 kg and 2.95 kg for patients treated with 2 mg and 4 mg twice daily of *Avandia*, respectively, versus 1.9 kg in glyburide-treated patients. In patients treated with *Avandia*, C-peptide, insulin, pro-insulin, and pro-insulin split products were significantly reduced in a dose-ordered fashion, compared to an increase in the glyburide-treated patients.

Combination with Metformin

A total of 670 patients with type 2 diabetes participated in two 26-week, randomized, double-blind, placebo/active-controlled studies designed to assess the efficacy of Avandia (rosiglitazone maleate) in combination with metformin. *Avandia*, administered in either once daily or twice daily dosing regimens, was added to the therapy of patients who were inadequately controlled on a maximum dose (2.5 grams/day) of metformin.

In one study, patients inadequately controlled on 2.5 grams/day of metformin (mean baseline FPG 216 mg/dL and mean baseline HbA1c 8.8%) were randomized to receive *Avandia* 4 mg once daily, *Avandia* 8 mg once daily, or placebo in addition to metformin. A statistically significant improvement in FPG and HbA1c was observed in patients treated with the combinations of metformin and *Avandia* 4 mg once daily and *Avandia* 8 mg once daily, versus patients continued on metformin alone (Table 4).

Table 4. Glycemic Parameters in a 26-Week Combination Study

	Metformin	*Avandia* 4 mg once daily + metformin	*Avandia* 8 mg once daily + metformin
N	113	116	110
FPG (mg/dL)			
Baseline (mean)	214	215	220
Change from baseline (mean)	6	−33	−48
Difference from metformin alone (adjusted mean)		−40*	−53*
Responders (≥30 mg/dL decrease from baseline)	20%	45%	61%
HbA1c (%)			
Baseline (mean)	8.6	8.9	8.9
Change from baseline (mean)	0.5	−0.6	−0.8
Difference from metformin alone (adjusted mean)		−1.0*	−1.2*
Responders (≥0.7% decrease from baseline)	11%	45%	52%

*<0.0001 compared to metformin.

In a second 26-week study, patients with type 2 diabetes inadequately controlled on 2.5 grams/day of metformin who were randomized to receive the combination of *Avandia* 4 mg twice daily and metformin (N=105) showed a statistically significant improvement in glycemic control with a mean treatment effect for FPG of –56 mg/dL and a mean treatment effect for HbA1c of –0.8% over metformin alone. The combination of metformin and *Avandia* resulted in lower levels of FPG and HbA1c than either agent alone. Patients who were inadequately controlled on a maximum dose (2.5 grams/day) of metformin and who were switched to monotherapy with Avandia (rosiglitazone maleate) demonstrated loss of glycemic control, as evidenced by increases in FPG and HbA1c. In this group, increases in LDL and VLDL were also seen.

Combination with a Sulfonylurea

A total of 1216 patients with type 2 diabetes participated in three 26-week randomized, double-blind, placebo/active-controlled studies designed to assess the efficacy and safety of *Avandia* in combination with a sulfonylurea. *Avandia* 2 mg or 4 mg daily, was administered either once daily or in divided doses twice daily, to patients inadequately controlled on a sulfonylurea.

In the two placebo-controlled studies, patients inadequately controlled on sulfonylureas that were randomized to single dose or divided doses of *Avandia* 4 mg daily plus a sulfonylurea showed significantly reduced FPG and HbA1c compared to sulfonylurea plus placebo (Table 5).

Table 5. Glycemic Parameters in Two 26-Week Combination Studies

Study C (patients on prior sulfonylurea monotherapy)	**Sulfonylurea**	***Avandia***
N	192	
FPG (mg/dL)		
Baseline (mean)	207	
Change from baseline (mean)	+6	
Difference from sulfonylurea alone (adjusted mean)	–	
Responders (≥30 mg/dL decrease from baseline)	21%	
HbA1c (%)		
Baseline (mean)	9.2	
Change from baseline (mean)	+0.2	
Difference from sulfonylurea alone (adjusted mean)	–	

Study D (patients on prior single or multiple therapies)	**Sulfonylurea**	***Avandia***
N	115	
FPG (mg/dL)		
Baseline (mean)	209	
Change from baseline (mean)	+23	
Difference from sulfonylurea alone (adjusted mean)	–	
Responders (≥30 mg/dL decrease from baseline)	13%	
HbA1c (%)		
Baseline (mean)	8.9	
Change from baseline (mean)	+0.6	
Difference from sulfonylurea alone (adjusted mean)	–	

*≤0.0001 compared to sulfonylurea plus placebo.

In the third study, including patients on prior single or multiple therapies, in patients inadequately controlled on maximal dose of glyburide (20 mg daily), *Avandia* 4 mg twice daily plus sulfonylurea significantly reduced FPG (n=98, mean change from baseline of –31 mg/dL) and HbA1c (mean change from baseline of –0.5%) compared to sulfonylurea plus placebo (n=99, mean change from baseline of +24 mg/dL and of HbA1c of +0.9%). The combination of sulfonylurea and *Avandia* resulted in lower levels of FPG and HbA1c than either agent alone. Patients who switched from maximal dose of glyburide to 2 mg twice daily *Avandia* monotherapy demonstrated loss of glycemic control, as evidenced by increases in FPG and HbA1c.

INDICATIONS AND USAGE

Avandia is indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus. *Avandia* is indicated as monotherapy. *Avandia* is also indicated for use in combination with a sulfonylurea, metformin when diet, exercise and a single agent do not result in adequate glycemic control. For patients inadequately controlled with a maximum dose of a sulfonylurea and metformin, *Avandia* should be added to, rather than substituted for, a sulfonylurea or metformin.

Management of type 2 diabetes should include diet and exercise. Caloric restriction, weight loss, and exercise are essential for the proper treatment of the diabetic patient because they help improve insulin sensitivity. This is important not only in the primary treatment of type 2 diabetes, but also in maintaining the efficacy of drug therapy. Prior to initiation of therapy with Avandia (rosiglitazone maleate), secondary causes of poor glycemic control, e.g., infection, should be investigated and treated.

CONTRAINDICATIONS

Avandia is contraindicated in patients with known hypersensitivity to this product or any of its components.

WARNINGS

Cardiac Failure and Other Cardiac Effects: *Avandia*, other thiazolidinediones, alone or in combination with

agents, can cause fluid retention, which may lead to heart failure. Patients should be observed for signs and symptoms of heart failure. *Avandia* should be discontinued if any deterioration in cardiac status occurs.

Patients with New York Heart Association (NYHA) Class 3 and 4 cardiac status were not studied during the clinical trials. *Avandia* is not recommended in patients with NYHA Class 3 and 4 cardiac status.

In two 26-week U.S. trials involving 611 patients with type 2 diabetes, *Avandia* plus insulin therapy was compared with insulin therapy alone. These trials included patients with long-standing diabetes and a high prevalence of pre-existing medical conditions, including peripheral neuropathy (19%), ischemic heart disease (14%), retinopathy (34%), cerebrovascular disease (9%), and congestive heart failure (2.5%). In these clinical studies an increased incidence of cardiac failure and other cardiovascular adverse events were seen in patients on *Avandia* and insulin combination therapy compared to insulin and placebo. Patients who experienced heart failure were on average older, had a longer duration of diabetes, and were mostly on the higher 8 mg daily dose of *Avandia*. In this population, however, it was not possible to determine specific risk factors that could be used to identify all patients at risk of heart failure on combination therapy. Three of 10 patients who developed cardiac failure on combination therapy during the double blind part of the studies had no known prior evidence of congestive heart failure, or pre-existing cardiac condition. **The use of Avandia (rosiglitazone maleate) in combination therapy with insulin is not indicated (see ADVERSE REACTIONS).**

PRECAUTIONS

General

Due to its mechanism of action, *Avandia* is active only in the presence of endogenous insulin. Therefore, *Avandia* should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis.

Hypoglycemia: Patients receiving *Avandia* in combination with other hypoglycemic agents may be at risk for hypoglycemia, and a reduction in the dose of the concomitant agent may be necessary.

Edema: *Avandia* should be used with caution in patients with edema. In a clinical study in healthy volunteers who received *Avandia* 8 mg once daily for 8 weeks, there was a statistically significant increase in median plasma volume compared to placebo.

Since thiazolidinediones, including rosiglitazone, can cause fluid retention, which can exacerbate or lead to congestive heart failure, *Avandia* should be used with caution in patients at risk for heart failure. Patients should be monitored for signs and symptoms of heart failure (see WARNINGS, Cardiac Failure and Other Cardiac Effects and PRECAUTIONS, Information for Patients).

In controlled clinical trials of patients with type 2 diabetes, mild to moderate edema was reported in patients treated with *Avandia*, and may be dose related. Patients with ongoing edema are more likely to have adverse events associated with edema if started on combination therapy with insulin and *Avandia* (see ADVERSE REACTIONS).

Weight Gain: Dose-related weight gain was seen with *Avandia* alone and in combination with other hypoglycemic agents (Table 6). The mechanism of weight gain is unclear but probably involves a combination of fluid retention and fat accumulation.

[Table at top right]

Hematologic: Across all controlled clinical studies, decreases in hemoglobin and hematocrit (mean decreases in individual studies ≤1.0 gram/dL and ≤3.3%, respectively) were observed for *Avandia* alone and in combination with other hypoglycemic agents. The changes occurred primarily during the first 3 months following initiation of *Avandia* therapy or following an increase in *Avandia* dose. White blood cell counts also decreased slightly in patients treated with *Avandia*. The observed changes may be related to the increased plasma volume observed with treatment with *Avandia* and may be dose related (see ADVERSE REACTIONS, Laboratory Abnormalities).

Ovulation: Therapy with *Avandia*, like other thiazolidinediones, may result in ovulation in some premenopausal anovulatory women. As a result, these patients may be at increased risk for pregnancy while taking *Avandia* (see PRECAUTIONS, Pregnancy, Pregnancy Category C). Adequate contraception in premenopausal women should be recommended. This possible effect has not been specifically investigated in clinical studies so the frequency of occurrence is not known.

Where hormonal imbalance has been seen in preclinical studies (see PRECAUTIONS, Carcinogenesis, Mutagenesis, Impairment of Fertility), the clinical significance of this finding is not known. If unexpected menstrual dysfunction occurs, the benefits of continued therapy with *Avandia* should be reviewed.

Hepatic Effects: Another drug of the thiazolidinedione class, troglitazone, was associated with idiosyncratic hepatotoxicity, and very rare cases of liver failure, liver transplant, and death were reported during clinical use. In pre-marketing controlled clinical trials in patients with type 2 diabetes, troglitazone was more frequently associated with clinically significant elevations in liver enzymes (ALT>3X upper limit of normal) compared to placebo. Very rare cases of hepatic jaundice were also reported.

Approximately 5000 clinical studies in 4598 patients treated with *Avandia*, encompassing approximately 3600 patient years of exposure, there was no signal of drug-induced hepatotoxicity or elevation of ALT levels. In the pre-approval controlled trials, 0.2% of patients treated with *Avandia* had elevations in ALT >3X the upper limit of normal compared to 0.2% on placebo and 0.5% on active comparators. The ALT elevations in patients treated with *Avandia* were reversible and were not clearly causally related to therapy with Avandia (rosiglitazone maleate).

In postmarketing experience with *Avandia*, reports of hepatitis and of hepatic enzyme elevations to three or more times the upper limit of normal have been received. Very rarely, these reports have involved hepatic failure with and without fatal outcome, although causality has not been established. Rosiglitazone is structurally related to troglitazone, a thiazolidinedione no longer marketed in the United States, which was associated with idiosyncratic hepatotoxicity and rare cases of liver failure, liver transplants, and death during clinical use. Pending the availability of the results of additional large, long-term controlled clinical trials and additional postmarketing safety data, it is recommended that patients treated with *Avandia* undergo periodic monitoring of liver enzymes.

Liver enzymes should be checked prior to the initiation of therapy with *Avandia* in all patients. Therapy with *Avandia* should not be initiated in patients with increased baseline liver enzyme levels (ALT>2.5X upper limit of normal). In patients with normal baseline liver enzymes, following initiation of therapy with *Avandia*, it is recommended that liver enzymes be monitored every 2 months for the first 12 months, and periodically thereafter. Patients with mildly elevated liver enzymes (ALT levels ≤2.5X upper limit of normal) at baseline or during therapy with *Avandia* should be evaluated to determine the cause of the liver enzyme elevation. Initiation of, or continuation of, therapy with *Avandia* in patients with mild liver enzyme elevations should proceed with caution and include close clinical follow-up, including more frequent liver enzyme monitoring, to determine if the liver enzyme elevations resolve or worsen. If at any time ALT levels increase to >3X the upper limit of normal in patients on therapy with *Avandia*, liver enzyme levels should be rechecked as soon as possible. If ALT levels remain >3X the upper limit of normal, therapy with *Avandia* should be discontinued.

There are no data available from clinical trials to evaluate the safety of *Avandia* in patients who experienced liver abnormalities, hepatic dysfunction, or jaundice while on troglitazone. Avandia (rosiglitazone maleate) should not be used in patients who experienced jaundice while taking troglitazone.

If any patient develops symptoms suggesting hepatic dysfunction, which may include unexplained nausea, vomiting, abdominal pain, fatigue, anorexia and/or dark urine, liver enzymes should be checked. The decision whether to continue the patient on therapy with *Avandia* should be guided by clinical judgment pending laboratory evaluations. If jaundice is observed, drug therapy should be discontinued.

Laboratory Tests

Periodic fasting blood glucose and HbA1c measurements should be performed to monitor therapeutic response.

Liver enzyme monitoring is recommended prior to initiation of therapy with *Avandia* in all patients and periodically thereafter (see PRECAUTIONS, *Hepatic Effects* and ADVERSE REACTIONS, Serum Transaminase Levels).

Information for Patients

Patients should be informed of the following:

Management of type 2 diabetes should include diet control. Caloric restriction, weight loss, and exercise are essential for the proper treatment of the diabetic patient because they help improve insulin sensitivity. This is important not only in the primary treatment of type 2 diabetes, but in maintaining the efficacy of drug therapy.

It is important to adhere to dietary instructions and to regularly have blood glucose and glycosylated hemoglobin tested. Patients should be advised that it can take 2 weeks to see a reduction in blood glucose and 2 to 3 months to see full effect. Patients should be informed that blood will be drawn to check their liver function prior to the start of therapy and every 2 months for the first 12 months, and periodically thereafter. Patients with unexplained symptoms of nausea, vomiting, abdominal pain, fatigue, anorexia, or dark urine should immediately report these symptoms to their physician. Patients who experience an unusually rapid increase in weight or edema or who develop shortness of breath or other symptoms of heart failure while on *Avandia* should immediately report these symptoms to their physician.

Avandia can be taken with or without meals.

When using *Avandia* in combination with other hypoglycemic agents, the risk of hypoglycemia, its symptoms and treatment, and conditions that predispose to its development should be explained to patients and their family members.

Therapy with *Avandia*, like other thiazolidinediones, may result in ovulation in some premenopausal anovulatory women. As a result, these patients may be at increased risk for pregnancy while taking *Avandia* (see PRECAUTIONS, Pregnancy, Pregnancy Category C). Thus, adequate contraception in premenopausal women should be recommended. This possible effect has not been specifically investigated in clinical studies so the frequency of occurrence is not known.

Drug Interactions

Drugs Metabolized by Cytochrome P_{450}

In vitro drug metabolism studies suggest that rosiglitazone does not inhibit any of the major P_{450} enzymes at clinically relevant concentrations. *In vitro* data demonstrate that rosiglitazone is predominantly metabolized by CYP2C8 and to a lesser extent, 2C9.

Avandia (4 mg twice daily) was shown to have no clinically relevant effect on the pharmacokinetics of nifedipine and oral contraceptives (ethinylestradiol and norethindrone), which are predominantly metabolized by CYP3A4.

Glyburide: Avandia (2 mg twice daily) taken concomitantly with glyburide (3.75 to 10 mg/day) for 7 days did not alter the mean steady-state 24-hour plasma glucose concentrations in diabetic patients stabilized on glyburide therapy.

Metformin: Concurrent administration of *Avandia* (2 mg twice daily) and metformin (500 mg twice daily) in healthy volunteers for 4 days had no effect on the steady-state pharmacokinetics of either metformin or rosiglitazone.

Acarbose: Coadministration of acarbose (100 mg three times daily) for 7 days in healthy volunteers had no clinically relevant effect on the pharmacokinetics of a single oral dose of *Avandia*.

Digoxin: Repeat oral dosing of *Avandia* (8 mg once daily) for 14 days did not alter the steady-state pharmacokinetics of digoxin (0.375 mg once daily) in healthy volunteers.

Warfarin: Repeat dosing with *Avandia* had no clinically relevant effect on the steady-state pharmacokinetics of warfarin enantiomers.

Ethanol: A single administration of a moderate amount of alcohol did not increase the risk of acute hypoglycemia in type 2 diabetes mellitus patients treated with Avandia (rosiglitazone maleate).

Ranitidine: Pretreatment with ranitidine (150 mg twice daily for 4 days) did not alter the pharmacokinetics of either single oral or intravenous doses of rosiglitazone in healthy volunteers. These results suggest that the absorption of oral rosiglitazone is not altered in conditions accompanied by increases in gastrointestinal pH.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis: A 2-year carcinogenicity study was conducted in Charles River CD-1 mice at doses of 0.4, 1.5, and 6 mg/kg/day in the diet (highest dose equivalent to approximately 12 times human AUC at the maximum recommended human daily dose). Sprague Dawley rats were dosed for 2 years by oral gavage at doses of 0.05, 0.3, and 2 mg/kg/day (highest dose equivalent to approximately 10 and 20 times human AUC at the maximum recommended human daily dose for male and female rats, respectively).

Rosiglitazone was not carcinogenic in the mouse. There was an increase in incidence of adipose hyperplasia in the mouse at doses ≥1.5 mg/kg/day (approximately 2 times human AUC at the maximum recommended human daily dose). In rats, there was a significant increase in the incidence of benign adipose tissue tumors (lipomas) at doses ≥0.3 mg/kg/day (approximately 2 times human AUC at the maximum

Continued on next page

Table 6: Weight Changes (kg) from Baseline During Clinical Trials with *Avandia*

Monotherapy	Duration	Control Group	Control Group Median (25^{th}, 75^{th} percentile)	*Avandia* 4 mg Median (25^{th}, 75^{th} percentile)	*Avandia* 8 mg Median (25^{th}, 75^{th} percentile)
	26 weeks	Placebo	–0.9 (–2.8, 0.9)	1.0 (–0.9, 3.6)	3.1 (1.1, 5.8)
	52 weeks	Sulfonylurea	2.0 (0, 4.0)	2.0 (–0.6, 4.0)	2.6 (0, 5.3)
Combination therapy					
sulfonylurea	26 weeks	Sulfonylurea	0 (–1.3, 1.2)	1.8 (0, 3.1)	—
metformin	26 weeks	Metformin	–1.4 (–3.2, 0.2)	0.8 (–1.0, 2.6)	2.1 (0, 4.3)
insulin	26 weeks	Insulin	0.9 (–0.5, 2.7)	4.1 (1.4, 6.3)	5.4 (3.4, 7.3)

This product information is based on labeling in effect on July 13, 2001. Further information is available at: GlaxoSmithKline, PO Box 13398, Research Triangle Park, NC 27709. 1-888-825-5249. Corporate Web Site: www.gsk.com

recommended human daily dose). These proliferative changes in both species are considered due to the persistent pharmacological overstimulation of adipose tissue.

Mutagenesis: Rosiglitazone was not mutagenic or clastogenic in the *in vitro* bacterial assays for gene mutation, the *in vitro* chromosome aberration test in human lymphocytes, the *in vivo* mouse micronucleus test, and the *in vivo*/*in vitro* rat UDS assay. There was a small (about 2-fold) increase in mutation in the *in vitro* mouse lymphoma assay in the presence of metabolic activation.

Impairment of Fertility: Rosiglitazone had no effects on mating or fertility of male rats given up to 40 mg/kg/day (approximately 116 times human AUC at the maximum recommended human daily dose). Rosiglitazone altered estrous cyclicity (2 mg/kg/day) and reduced fertility (40 mg/kg/day) of female rats in association with lower plasma levels of progesterone and estradiol (approximately 20 and 200 times human AUC at the maximum recommended human daily dose, respectively). No such effects were noted at 0.2 mg/kg/day (approximately 3 times human AUC at the maximum recommended human daily dose). In monkeys, rosiglitazone (0.6 and 4.6 mg/kg/day; approximately 3 and 15 times human AUC at the maximum recommended human daily dose, respectively) diminished the follicular phase rise in serum estradiol with consequential reduction in the luteinizing hormone surge, lower luteal phase progesterone levels, and amenorrhea. The mechanism for these effects appears to be direct inhibition of ovarian steroidogenesis.

Animal Toxicology

Heart weights were increased in mice (3 mg/kg/day), rats (5 mg/kg/day), and dogs (2 mg/kg/day) with rosiglitazone treatments (approximately 5, 22, and 2 times human AUC at the maximum recommended human daily dose, respectively). Morphometric measurement indicated that there was hypertrophy in cardiac ventricular tissues, which may be due to increased heart work as a result of plasma volume expansion.

Pregnancy

Pregnancy Category C

There was no effect on implantation or the embryo with rosiglitazone treatment during early pregnancy in rats, but treatment during mid-late gestation was associated with fetal death and growth retardation in both rats and rabbits. Teratogenicity was not observed at doses up to 3 mg/kg in rats and 100 mg/kg in rabbits (approximately 20 and 75 times human AUC at the maximum recommended human daily dose, respectively). Rosiglitazone caused placental pathology in rats (3 mg/kg/day). Treatment of rats during gestation through lactation reduced litter size, neonatal viability, and postnatal growth, with growth retardation reversible after puberty. For effects on the placenta, embryo/fetus, and offspring, the no-effect dose was 0.2 mg/kg/day in rats and 15 mg/kg/day in rabbits. These no-effect levels are approximately 4 times human AUC at the maximum recommended human daily dose.

There are no adequate and well-controlled studies in pregnant women. Avandia (rosiglitazone maleate) should not be used during pregnancy unless the potential benefit justifies the potential risk to the fetus.

Because current information strongly suggests that abnormal blood glucose levels during pregnancy are associated with a higher incidence of congenital anomalies as well as increased neonatal morbidity and mortality, most experts recommend that insulin monotherapy be used during pregnancy to maintain blood glucose levels as close to normal as possible.

Labor and Delivery

The effect of rosiglitazone on labor and delivery in humans is not known.

Nursing Mothers

Drug-related material was detected in milk from lactating rats. It is not known whether *Avandia* is excreted in human milk. Because many drugs are excreted in human milk, *Avandia* should not be administered to a nursing woman.

ADVERSE REACTIONS

In clinical trials, approximately 4600 patients with type 2 diabetes have been treated with *Avandia*; 3300 patients were treated for 6 months or longer and 2000 patients were treated for 12 months or longer.

Trials of *Avandia* as Monotherapy and in Combination with Other Hypoglycemic Agents

The incidence and types of adverse events reported in clinical trials of *Avandia* as monotherapy are shown in Table 7. [See table at bottom of page]

There were a small number of patients treated with *Avandia* who had adverse events of anemia and edema. Overall, these events were generally mild to moderate in severity and usually did not require discontinuation of treatment with Avandia (rosiglitazone maleate).

In double-blind studies, anemia was reported in 1.9% of patients receiving *Avandia* compared to 0.7% on placebo, 0.6% on sulfonylureas and 2.2% on metformin. Edema was reported in 4.8% of patients receiving *Avandia* compared to 1.3% on placebo, 1.0% on sulfonylureas, and 2.2% on metformin. Overall, the types of adverse experiences reported when *Avandia* was used in combination with a sulfonylurea or metformin were similar to those during monotherapy with *Avandia*. Reports of anemia (7.1%) were greater in patients treated with a combination of *Avandia* and metformin compared to monotherapy with *Avandia* or in combination with a sulfonylurea.

Lower pre-treatment hemoglobin/hematocrit levels in patients enrolled in the metformin combination clinical trials may have contributed to the higher reporting rate of anemia in these studies (see ADVERSE REACTIONS, Laboratory Abnormalities, Hematologic).

In 26-week double-blind studies, edema was reported with higher frequency in the *Avandia* plus insulin combination trials (insulin, 5.4%, and *Avandia* in combination with insulin, 14.7%). Reports of new onset or exacerbation of congestive heart failure occurred at rates of 1% for insulin alone, and 2% (4 mg) and 3% (8 mg) for insulin in combination with *Avandia* (see WARNINGS, Cardiac Failure and Other Cardiac Effects).

In postmarketing experience with *Avandia*, adverse events potentially related to volume expansion (e.g., congestive heart failure, pulmonary edema, and pleural effusions) have been reported.

Laboratory Abnormalities

Hematologic: Decreases in mean hemoglobin and hematocrit occurred in a dose-related fashion in patients treated with *Avandia* (mean decreases in individual studies up to 1.0 gram/dL hemoglobin and up to 3.3% hematocrit). The time course and magnitude of decreases were similar in patients treated with a combination of *Avandia* and other hypoglycemic agents or *Avandia* monotherapy. Pre-treatment levels of hemoglobin and hematocrit were lower in patients in metformin combination studies and may have contributed to the higher reporting rate of anemia. White blood cell counts also decreased slightly in patients treated with *Avandia*. Decreases in hematologic parameters may be related to increased plasma volume observed with treatment with *Avandia*.

Lipids: Changes in serum lipids have been observed following treatment with *Avandia* (see CLINICAL STUDIES).

Serum Transaminase Levels: In clinical studies in 4598 patients treated with Avandia (rosiglitazone maleate) encompassing approximately 3600 patient years of exposure, there was no evidence of drug-induced hepatotoxicity or elevated ALT levels.

In controlled trials, 0.2% of patients treated with *Avandia* had reversible elevations in ALT >3X the upper limit of normal compared to 0.2% on placebo and 0.5% on active comparators. Hyperbilirubinemia was found in 0.3% of patients treated with *Avandia* compared with 0.9% treated with placebo and 1% in patients treated with active comparators.

In the clinical program including long-term, open-label experience, the rate per 100 patient years exposure of ALT increase to >3X the upper limit of normal was 0.35 for patients treated with *Avandia*, 0.59 for placebo-treated patients, and 0.78 for patients treated with active comparator agents.

In pre-approval clinical trials, there were no cases of idiosyncratic drug reactions leading to hepatic failure. In postmarketing experience with Avandia (rosiglitazone maleate), reports of hepatic enzyme elevations three or more times the upper limit of normal and hepatitis have been received (see PRECAUTIONS, Hepatic Effects).

DOSAGE AND ADMINISTRATION

The management of antidiabetic therapy should be individualized. *Avandia* may be administered either at a starting dose of 4 mg as a single daily dose or divided and administered in the morning and evening. For patients who respond inadequately following 8 to 12 weeks of treatment, as determined by reduction in FPG, the dose may be increased to 8 mg daily as indicated below. Reductions in glycemic parameters by dose and regimen are described under CLINICAL STUDIES. *Avandia* may be taken with or without food.

Monotherapy

The usual starting dose of *Avandia* is 4 mg administered either as a single dose once daily or in divided doses twice daily. In clinical trials, the 4 mg twice daily regimen resulted in the greatest reduction in FPG and HbA1c.

Combination Therapy with a Sulfonylurea or Metformin

When *Avandia* is added to existing therapy, the current dose of sulfonylurea or metformin can be continued at initiation of *Avandia* therapy.

Sulfonylurea:

When used in combination with sulfonylurea, the recommended dose of *Avandia* is 4 mg administered as either a single dose once daily or in divided doses twice daily. If patients report hypoglycemia, the dose of the sulfonylurea should be decreased.

Metformin:

The usual starting dose of *Avandia* in combination with metformin is 4 mg administered as either a single dose once daily or in divided doses twice daily. It is unlikely that the dose of metformin will require adjustment due to hypoglycemia during combination therapy with *Avandia*.

Maximum Recommended Dose:

The dose of *Avandia* should not exceed 8 mg daily, as a single dose or divided twice daily. The 8 mg daily dose has been shown to be safe and effective in clinical studies as monotherapy and in combination with metformin. Doses of *Avandia* greater than 4 mg daily in combination with a sulfonylurea have not been studied in adequate and well-controlled clinical trials.

Avandia may be taken with or without food.

No dosage adjustments are required for the elderly.

No dosage adjustment is necessary when *Avandia* is used as monotherapy in patients with renal impairment. Since metformin is contraindicated in such patients, concomitant administration of metformin and *Avandia* is also contraindicated in patients with renal impairment.

Therapy with *Avandia* should not be initiated if the patient exhibits clinical evidence of active liver disease or increased serum transaminase levels (ALT >2.5X upper limit of normal at start of therapy) (see PRECAUTIONS, *Hepatic Effects* and CLINICAL PHARMACOLOGY, Hepatic Impairment). Liver enzyme monitoring is recommended in all patients prior to initiation of therapy with *Avandia*, and periodically thereafter (see PRECAUTIONS, *Hepatic Effects*).

There are no data on the use of *Avandia* in patients under 18 years of age; therefore, use of *Avandia* in pediatric patients is not recommended.

OVERDOSAGE

Limited data are available with regard to overdosage in humans. In clinical studies in volunteers, Avandia (rosiglitazone maleate) has been administered at single oral doses of up to 20 mg and was well-tolerated. In the event of an overdose, appropriate supportive treatment should be initiated as dictated by the patient's clinical status.

HOW SUPPLIED

Tablets: Each pentagonal film-coated Tiltab® tablet contains rosiglitazone as the maleate as follows: 2 mg-pink, debossed with SB on one side and 2 on the other; 4 mg-orange, debossed with SB on one side and 4 on the other; 8 mg—red-brown, debossed with SB on one side and 8 on the other.

2 mg bottles of 30: NDC 0029-3158-13
2 mg bottles of 60: NDC 0029-3158-18
2 mg bottles of 100: NDC 0029-3158-20
2 mg bottles of 500: NDC 0029-3158-25
2 mg SUP 100s: NDC 0029-3158-21
4 mg bottles of 30: NDC 0029-3159-13
4 mg bottles of 60: NDC 0029-3159-18
4 mg bottles of 100: NDC 0029-3159-20
4 mg bottles of 500: NDC 0029-3159-25
4 mg SUP 100s: NDC 0029-3159-21
8 mg bottles of 30: NDC 0029-3160-13
8 mg bottles of 100: NDC 0029-3160-20
8 mg bottles of 500: NDC 0029-3160-25
8 mg SUP 100s: NDC 0029-3160-21

STORAGE

Store at 25°C (77°F), excursions 15°–30°C (59°–86°F). Dispense in a tight, light-resistant container.

February 2001/AV:L6

Shown in Product Identification Guide, page 314

Table 7. Adverse Events (≥5% in Any Treatment Group) Reported by Patients in Double-blind Clinical Trials with *Avandia* as Monotherapy

Preferred Term	*Avandia* Monotherapy N = 2526 %	Placebo N = 601 %	Metformin N = 225 %	Sulfonylureas* N = 626 %
Upper respiratory tract infection	9.9	8.7	8.9	7.3
Injury	7.6	4.3	7.6	6.1
Headache	5.9	5.0	8.9	5.4
Back pain	4.0	3.8	4.0	5.0
Hyperglycemia	3.9	5.7	4.4	8.1
Fatigue	3.6	5.0	4.0	1.9
Sinusitis	3.2	4.5	5.3	3.0
Diarrhea	2.3	3.3	15.6	3.0
Hypoglycemia	0.6	0.2	1.3	5.9

*Includes patients receiving glyburide (N=514), gliclazide (N=91) or glipizide (N=21).

BACTROBAN CREAM®
[back 'trō-ban]
brand of
mupirocin calcium cream, 2%
For Dermatologic Use

DESCRIPTION

Bactroban Cream (mupirocin calcium cream), 2% contains the dihydrate crystalline calcium hemisalt of the antibiotic